National Collaborating Centre for Acute Care
at The Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London WC2A 3PE T: 020 7869 6630 F: 020 7869 6639

# Venous Thromboembolism

## Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery.

**Commissioned by the National Institute for Health and Clinical Excellence**

Published by the National Collaborating Centre for Acute Care at The Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London, WC2A 3PE

First published 2007



ISBN 0-9549760-3-7

Front cover image: ©Vasiliy Yakobchuk. BigStockPhoto.com

# Foreword

The second report of session 2004-5 of The House of Commons Health Committee 'The Prevention of Venous Thromboembolism in Hospitalised Patients' opens with these worrying statistics: Each year 25,000 people in England die from venous thromboembolism. This figure includes both patients admitted for medical care of serious illnesses as well as those admitted for surgery. The report goes on to state that this is a larger number of deaths than are attributable to breast cancer, AIDS and road traffic accidents. It is 25 times the number of people who die as a result of MRSA infection[246].

The sudden killer is pulmonary embolism (PE), that is a thrombus (or blood clot) which formed in the lower limb or pelvic veins and then comes loose to be carried in the blood to lodge in the lungs. Acute massive pulmonary embolism often kills immediately. If the patient survives the immediate haemodynamic consequences, death may still ensue in the days or weeks that follow. Eventual survivors may well have been in intensive care and may follow a protracted hospital course to recovery.

Deep vein thrombosis (DVT) is in itself a cause of substantial morbidity and may lead to the development of post-phlebetic syndrome with chronic swelling and ulceration of the legs amongst its manifestations. Add this burden of morbidity to the 25,000 deaths and it becomes a massive health problem.

Many of these deaths are in patients admitted for medical care but some have gone into hospital for a planned surgery such as joint replacement, gynaecological surgery or gall bladder removal to improve their quality of life, or a cancer surgery with the hope of cure. It is characteristically a week or two after surgery, when recovery is in sight that this tragedy strikes. Our guideline covers patients having surgery that requires an overnight stay. Minor operations performed as day cases or out of hospital are therefore not included. This includes the large number of routine planned operations.

The degree of risk of venous thromboembolism (VTE) is dependent upon factors inherent in the operation and factors related to the individual patient. It is the combination of these factors which defines certain patients as at increased risk of VTE.

Surgeons have been acutely aware of this problem and have been central to research from the 1970's and 1980's. Physical methods (such as graduated compression stockings and intermittent pneumatic compression) and pharmacological treatments (such as dextran infusion, heparin and warfarin) have been studied in a plethora of randomised trials. Both physical and pharmacological treatments have been shown to reduce the incidence of DVT under study conditions. The difficulty is knowing how to implement prophylaxis in practice. Will reduction of DVTs translate into reduced death rates from PE?

There is a question over whether the incidence of PE bears a reasonably consistent numerical relationship to the more frequent DVT. We have not made this an assumption but have tested the hypothesis, where data sets allow both to be counted. There is a close association.

The next question is whether the reduction in DVT (the more numerous and thus the more easily studied adverse outcome) will result in a proportionate reduction in potentially fatal PE. Again we have not simply assumed this but tested the extrapolation against the data. As an extra degree of caution we have tested our recommendations by performing sensitivity analyses where we rely on this extrapolation.

The pharmacological methods introduce another consideration. They carry with them a new risk of bleeding. The bleeding complications are clinically important and are counted in the RCTs. We have to set protocols that chart the safest course for the most of patients between the competing risks posed to them of thrombosis on the one hand and bleeding on the other.

It appears to us to be a clinical problem which requires a meticulously researched and analysed evidence base. The potential health gains for the optimum strategy are great. An individual team will have patients who suffer PE and patients whose recovery is complicated by a treatment related bleed. The clinical difficulty is that both venous thromboembolism and bleeding have low event rates affecting fewer than one in a hundred patients. We cannot emphasise too strongly that it is evidence from the best available randomised controlled trials that we must use to quantify these competing risks. It is well known that if clinicians base decisions for future patients on a recent adverse event, the decisions are unlikely to be in the best interest of those future patients[98].

The impossibility of basing a policy on clinical experience makes it essential to rely on evidence based guidance. It is appropriate this guidance is made available for individual clinicians and their teams to use in framing locally implemented prophylactic policies. This is an ideal subject for an evidence based guideline. The complex task has been undertaken in collaboration between the scientific staff at the NCC-AC and the medical professionals of the Guideline Development Group (GDG).

Some of our recommendations are more conservative than might be expected from a reading of other guidelines, for example avoidance of heparin in some groups. It is because we find that the loss of health due to bleeding outweighs the gains attributable to a pharmacological treatment.

A summary of our recommendations:

Mechanical methods such as the use of graduated compression/anti-embolism stockings are effective and do not add the risk of bleeding. We have recommended these methods for most patients.

At higher risk of VTE, the use of a pharmacological method (usually low molecular weight heparin or fondaparinux) is cost effective. This is to be used against a background of mechanical prophylaxis such as stockings (as was the case in many of the RCTs on which we rely).

There will be surgical patients who are already on antiplatelet medication; there will also be some for whom aspirin may be recommended in the perioperative period for the reduction of risk of heart attack and stroke. This may present a therapeutic conflict. It should be noted that while aspirin does reduce the risk of VTE to some extent, we have not recommended it as a form of VTE prophylaxis. Aspirin has an important role in cardiovascular perioperative risk reduction but this is outside our scope. It might be tempting to see antiplatelet therapy as a convenient prophylactic "two for one". To use this as a clinical justification for omitting recommended VTE pharmacological prophylaxis risks reducing the effectiveness of VTE prophylaxis and we have not tested the effectiveness or cost effectiveness of that strategy. It would have to be a matter of case by case clinical judgement: we can go no further than the VTE prophylaxis recommended in the guidelines.

Although there are many trials we still found ourselves with uncertainties. For example the true present day rate of DVT and PE is very hard to ascertain. Many more patients have less invasive surgery. Surgical patients get out of bed sooner. High emphasis is placed on early mobilisation and early discharge from hospital. Prophylaxis (both mechanical and pharmacological) is widely used by surgeons and may be having an impact but practices may vary and implantation is probably patchy. There is a strong sense that DVT and PE are less of a problem than they used to be in surgical patients but maybe it is hidden from the view of clinicians by early discharge rather than being truly reduced.

High quality monitoring of adverse events will be needed to ensure that these recommendations are as safe as they can be and we emphasise strongly the need to implement the research recommendations. These research recommendations specifically target the area where we found the biggest potential consequence from uncertainty. We also welcome the recommendation of the House of Commons Health Committee: "Systems must be put in place to ensure that the NICE VTE guidelines are implemented"[246]. Once implemented, we need to monitor adverse events, both bleeding and venous thromboembolism to ensure that guidance is steering the safest course between those competing risks to surgical patients.

Professor Tom Treasure

Chair, Guideline Development Group

# Contents

**APPENDICES**

Appendices can be found in a separate document.

# Guideline Development Group membership and acknowledgments

## Guideline Development Group

| | |
|---|---|
| Professor Tom Treasure (Chair) | Consultant Thoracic Surgeon, Guys Hospital, London |
| Mr Nigel Acheson | Consultant Gynaecological Oncologist, Royal Devon & Exeter Hospital |
| Dr Ricky Autar | Clinical Nurse Consultant, University Hospitals of Leicester NHS trust & Principal Lecturer in Nursing, De Montfort University |
| Professor Colin Baigent | Clinical Epidemiologist, Clinical Trial Service Unit (CTSU), Oxford |
| Mrs Kim Carter | DVT Nurse Specialist, Portsmouth Hospitals NHS Trust, Queen Alexandra Hospital, Portsmouth |
| Mr Simon Carter | Consultant Orthopaedic Oncologist, Royal Orthopaedic Hospital, Birmingham |
| Mr David Farrell | Patient Representative |
| Dr David Goldhill | Consultant Anaesthestist, The Royal National Orthopaedic Hospital, Stanmore |
| Dr John Luckit | Consultant Haematologist, North Middlesex University Hospital |
| Mr Robin Offord | Director of Clinical Pharmacy, University College Hospital, London |
| Mr Adam Thomas | Patient Representative |

## NCC-AC staff on the Guideline Development Group

| | |
|---|---|
| Dr Jennifer Hill | Director of NCC-AC / Project Manager |
| Dr Philippa Davies | Research Associate / Project Manager |
| Dr Saoussen Ftouh | Project Manager (from October 2006) |
| Mr Enrico De Nigris | Health Economist |
| Mr Peter B Katz | Information Scientist |
| Mr Carlos Sharpin | Information Scientist / Research Associate |
| Mr David Wonderling | Senior Health Economist |
| Dr Arash Rashidian | Methodological Advisor |

## Acknowledgements

The development of this guideline was greatly assisted by the following people:

> NCC-AC

Funsho Akinluyi, Rifna Aktar, Gianluca Baio, Sophie Capo-Bianco, Kelly Dickinson, Clare Jones, Susan Murray, Kathryn Oliver, Veena Mazarello Paes, Jacqueline Rainsbury, Nishanthi Tallawila, Louise Thomas, Jennifer Wood.

> Expert Advisors

John Black, Jonathan Emberson, Mark Emberton, Nihal Gurusinghe, Tim Lees, Frank Smith, Sir Peter Morris, David Whillier.

## Guideline Review Panel

The Guideline Review Panel is an independent panel that overseas the development of the guideline and takes responsibility for monitoring its quality. The members of the Guideline Review Panel were as follows:

**Mr Peter Robb (Chair)**

Consultant ENT Surgeon, Epsom and St Helier University Hospitals and The Royal Surrey County NHS Trusts

**Mrs Jill Freer**

Director of Patient Services, Rugby PCT

**Mr John Seddon**

Patient representative

**Dr John Young**

Medical Director, Merck Sharp & Dohme Ltd

# Stakeholder Involvement

## The following stakeholders registered with NICE and were invited to comment on draft versions of these guidelines

:

•Activa Healthcare Ltd
• Addenbrooke's NHS Trust
• Age Concern Cymru
• Airedale General Hospital
• Amdipharm PLC
• AMORE Studies Group
• Amtec Medical Ltd
• Anaesthetic Office
• Anglesey Local Health Board
• Anticoagulation Europe
• Anticoagulation Specialist Association
• Ashfield and Mansfield District PCT
• Association of British Health-Care Industries
• Association of Plastic Surgeons
• Association of Surgeons of Great Britain and Ireland
• Association of the British Pharmaceuticals Industry (ABPI)
• AstraZeneca UK Ltd
• Aventis Pharma
• Bard Limited
• Barnet PCT
• Barnsley Acute Trust
• Barnsley PCT
• Bayer Healthcare
• Bedfordshire & Hertfordshire NHS Strategic Health Authority
• Birmingham Heartlands & Solihull NHS Trust
• Boehringer Ingelheim Ltd
• Bradford PCT
• Bradford Teaching Hospitals Trust
• Bristol-Myers Squibb Pharmaceuticals Ltd
• British Association for Surgery of the Knee
• British Association of Plastic Surgeons
• British Association of Stroke Physicians
• British Association of Urological Surgeons
• British Cardiac Society
• British Cardiovascular Society
• British Committee for Standards in Haematology
• British Geriatrics Society
• British Heart Foundation
• British Hip Society
• British Lymphology Society
• British Maternal and Fetal Medicine Society
• British Menopause Society
• British National Formulary (BNF)
• British Orthopaedic Association
• British Psychological Society
• British Society of Interventional Radiology
• British Thoracic Society
• British Trauma Society
• Buckinghamshire Hospitals NHS Trust
• Cardiff and Vale NHS Trust
• CASPE
• Central Liverpool PCT
• Central Manchester PCT
• Chartered Society of Physiotherapy
• Chesterfield PCT
• Chronic Conditions Collaborating Centre
• City Hospitals Sunderland NHS Trust
• Clinical Effectiveness Committee
• Commission for Social Care Inspection
• Connecting for Health
• Conwy & Denbighshire NHS Trust
• Co-operative Pharmacy Association
• Cotswold and Vale PCT
• Countess of Chester Hospital NHS Foundation Trust
• David Lewis Centre
• Department of Health
• Dudley Group of Hospitals NHS Trust
• East and North Hertfordshire NHS Trust
• East Cambridgeshire and Fenland PCT
• English Community Care Association
• Faculty of Dental Surgery
• Faculty of Family Planning and Reproductive Health Care
• Faculty of Public Health
• Fibroid Network Charity
• Gateshead Health NHS Trust
• GlaxoSmithKline UK Ltd
• Gloucestershire Hospitals NHS Trust
• Good Hope NHS Trust
• Greater Peterborough Primary Care Partnership-North PCT
• Guys & St Thomas NHS Trust
• Hammersmith Hospitals NHS Trust
• Health Protection Agency
• Health Protection Scotland
• Healthcare Commission
• Heart of England NHS Foundation Trust
• Heatherwood and Wexham Park Hospitals Trust
• Hospital Alvarez
• Huntleigh Healthcare Ltd
• Independent Healthcare Advisory Service
• Independent Healthcare Forum
• Intensive Care Society
• Intavent Orthofix Ltd
• Kimal Plc
• King's College Hospital NHS Trust
• Leeds Teaching Hospitals NHS Trust
• LEO pharma
• LifeBlood: The Thrombosis Charity
• Liverpool PCT
• Luton and Dunstable Hospital NHS Trust
• Maidstone and Tunbridge Wells NHS Trust
• Mansfield District PCT

- Medicines and Healthcare Products Regulatory Agency (MHRA)
- Medlock Medical
- Medway NHS Trust, The
- Mental Health Collaborating Centre
- Mid Staffordshire General Hospitals NHS Trust
- Musgrave Park Hospital
- National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)
- National Patient Safety Agency
- National Pre-Assessment Project
- National Public Health Service – Wales
- NCC for Cancer
- NCCHTA
- NHS Direct
- NHS Health and Social Care Information Centre
- NHS Pathways
- NHS Quality Improvement Scotland
- Niger Delta University
- Norfolk and Norwich University Hospital NHS Trust
- North Eastern Derbyshire PCT
- North Glamorgan NHS Trust – Merthyr Tydfil
- North Middlesex University Hospital NHS Trust
- North Staffordshire Combined Healthcare NHS Trust
- North Tees and Hartlepool NHS Trust
- Northwest London Hospitals NHS Trust
- Nuffield Hospitals Acute Care
- Nuffield Orthopaedic Centre NHS Trust
- Nursing & Supportive Care Collaborating Centre
- Organon Laboratories Ltd
- Orthofix Vascular Novamedix
- Pancreatic Cancer UK
- PERIGON (formerly the NHS Modernisation Agency)
- Pfizer Ltd
- Prodigy
- Powys Local Health Board
- Primary Care Collaborating Centre
- Princess Alexandra Hospital NHS Trust
- Queen Elizabeth NHS Trust
- Queen Mary's NHS Trust
- Queen Victoria Hospital NHS Foundation Trust
- Regional Public Health Group – London
- RCM Consultant Midwives Forum
- Regional Public Health Group - London
- Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS, The
- Roche Diagnostics Ltd
- Rotherham PCT
- Royal Brompton and Harefield NHS Trust
- Royal College of Anaesthetists
- Royal College of General Practitioners
- Royal College of General Practitioners Wales
- Royal College of Midwives
- Royal College of Nursing (RCN)
- Royal College of Obstetricians & Gynaecologists
- Royal College of Pathologists
- Royal College of Physicians of London
- Royal College of Surgeons of England
- Royal National Orthopaedic Hospital NHS Trust
- Royal Society of Medicine
- Royal United Hospital, Bath NHS Trust
- Royal West Sussex Trust , The
- Sanofi-Aventis
- Scottish Intercollegiate Guidelines Network (SIGN)
- Sheffield Children's Hospital NHS Trust
- Sheffield South West PCT
- Sheffield Teaching Hospitals NHS Trust
- Sigvaris Britain Ltd
- Society and College of Radiographers
- South Devon Healthcare Trust
- South East Sheffield PCT
- South Manchester University Hospitals NHS Trust
- SSL International Plc
- Staffordshire Ambulance HQ
- Staffordshire Moorlans PCT
- Stockport PCT
- Talley Group Ltd
- Tameside and Glossop Acute Services NHS Trust
- Tissue Viability Society (UK)
- Trafford PCT
- Translucency Ltd
- Tyco Healthcare
- UK Clinical Pharmacy Association
- UK Specialised Services Public health Network
- University College London Hospitals NHS Trust
- University Hospital Birmingham NHSFT
- University of Hertfordshire
- Urgo Ltd
- Wareney PCT
- Welsh Assembly Government (formerly National Assembly for Wales)
- Welsh Scientific Advisory Committee (WSAC)
- West of Cornwall PCT
- Women's & Children's Collaborating Centre
- Women's Health Concern

# Abbreviations

| | |
|---|---|
| **BNF** | British National Formulary |
| **CCA** | Cost-consequences analysis |
| **CEA** | Cost-effectiveness analysis |
| **CI** | Confidence interval |
| **CPM** | Continuous passive motion |
| **CUA** | Cost-utility analysis |
| **DH** | Department of Health |
| **DVT** | Deep-vein thrombosis |
| **ES** | Electrical stimulation |
| **FID** | Foot impulse device |
| **GCS** | Graduated compression stocking |
| **GDG** | Guideline Development Group |
| **GP** | General Practitioner |
| **GRADE** | Guidelines Recommendations Assessment Development Evaluation |
| **GRP** | Guideline Review Panel |
| **HES** | Hospital Episode Statistics |
| **HIT** | Heparin-induced thrombocytopenia |
| **HRQL** | Health-related quality of life |
| **HTA** | Health technology assessment |
| **ICER** | Incremental cost-effectiveness ratio |
| **INB** | Incremental net benefit |
| **INR** | International normalised ratio |
| **IPC** | Intermittent pneumatic compression |
| **IV** | Intravenous |
| **LMWH** | Low molecular weight heparin |
| **LOS** | Length of Stay |
| **LY** | Life-year |

| | |
|---|---|
| **MHRA** | Medicines and Healthcare Products Regulatory Agency |
| **MTC** | Mixed-treatment comparisons |
| **NCC-AC** | National Collaborating Centre for Acute Care |
| **NHS** | National Health Service |
| **NICE** | National Institute for Health and Clinical Excellence |
| **NNT** | Number needed to treat |
| **OAC** | Oral anticoagulants |
| **OR** | Odds ratio |
| **PASA** | NHS Purchasing and Supply Agency |
| **PE** | Pulmonary embolism |
| **PICO** | Framework incorporating patients, interventions, comparisons, outcomes |
| **PPIP** | Patient and Public Involvement Programme |
| **PSA** | Probabilistic sensitivity analysis |
| **PTS** | Post-thrombotic syndrome |
| **QALY** | Quality-adjusted life year |
| **RCT** | Randomised controlled trial |
| **RR** | Relative risk |
| **sc** | Subcutaneous |
| **SR** | Systematic review |
| **UFH** | Unfractionated heparin |
| **vs** | Versus |
| **VT** | Venous thrombosis |
| **VTE** | Venous thromboembolism |

# Glossary of Terms

| | |
|---|---|
| **Absolute risk reduction (Risk difference)** | The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study. |
| **Abstract** | Summary of a study, which may be published alone or as an introduction to a full scientific paper. |
| **Adjustment** | A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods. |
| **Algorithm (in guidelines)** | A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows. |
| **Allocation concealment** | The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants. |
| **Anticoagulants** | Any agent used to prevent the formation of blood clots. These include oral agents, such as warfarin, and others which are injected into a vein or under the skin, such as heparin. |
| **Applicability** | The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting. |
| **Appraisal of Guidelines, Research and Evaluation (AGREE)** | An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines. |
| **Arm (of a clinical study)** | Sub-section of individuals within a study who receive one particular intervention, for example placebo arm. |
| **Association** | Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal. |
| **Audit** | See 'Clinical audit'. |
| **Baseline** | The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared. |
| **Bias** | Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted. |
| **Blinding (masking)** | Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study |
| **Capital costs** | Costs of purchasing major capital assets (usually land, buildings or equipment). Capital costs represent investments at one point in time. |
| **Carer (caregiver)** | Someone other than a health professional who is involved in caring for a person with a medical condition. |
| **Case-control study** | Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause. |
| **Case series** | Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients. |

| | |
|---|---|
| **Clinical audit** | A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. |
| **Clinical efficacy** | The extent to which an intervention is active when studied under controlled research conditions. |
| **Clinical effectiveness** | The extent to which an intervention produces an overall health benefit in routine clinical practice. |
| **Clinical impact** | The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes, of the target population. |
| **Clinical question** | In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations. |
| **Clinician** | A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist. |
| **Cluster** | A closely grouped series of events or cases of a disease or other related health phenomena with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation. |
| **Cochrane Library** | A regularly updated electronic collection of evidence-based medicine databases, including the Cochrane Database of Systematic Reviews. |
| **Cochrane Review** | A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library. |
| **Cohort study** | A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest. |
| **Co-morbidity** | Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual. |
| **Comparability** | Similarity of the groups in characteristics likely to affect the study results (such as health status or age). |
| **Compliance** | The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'. |
| **Conference proceedings** | Compilation of papers presented at a conference. |
| **Confidence interval (CI)** | A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value. |
| **Confounding** | In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study. |
| **Consensus methods** | Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field. |
| **Control group** | A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug. |
| **Controlled clinical trial (CCT)** | A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an |

| | |
|---|---|
| | alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a *randomised controlled trial*. |
| **Cost benefit analysis** | A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment. |
| **Cost-consequences analysis (CCA)** | A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain. |
| **Cost-effectiveness analysis (CEA)** | An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness. |
| **Cost-effectiveness model** | An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes. |
| **Cost-utility analysis (CUA)** | A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs). |
| **Continuous passive motion** | Where a joint is moved continuously, either by another person bending it or by a machine. |
| **Credible interval** | The Bayesian equivalent of a confidence interval. |
| **Decision analysis** | A systematic way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes. |
| **Decision analytic techniques** | A way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees that direct the clinician through a succession of possible scenarios, actions and outcomes. |
| **Decision problem** | A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform. |
| **Deep-vein thrombosis (DVT)** | Venous thrombosis that occurs in the "deep veins" in the legs, thighs, or pelvis. |
| **Discounting** | Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present. |
| **Distal** | Refers to a part of the body that is farther away from the centre of the body than another part. |
| **Dominance** | An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective. |
| **Dosage** | The prescribed amount of a drug to be taken, including the size and timing of the doses. |
| **Double blind study** | A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment nor intervention the subject is receiving. The purpose of blinding is to protect against bias. |
| **DVT** | See 'Deep-vein thrombosis'. |
| **Drop-out** | A participant who withdraws from a clinical trial before the end. |

| | |
|---|---|
| **Economic evaluation** | Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences. |
| **Effect (as in effect measure, treatment effect, estimate of effect, effect size)** | The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association. |
| **Effectiveness** | See 'Clinical effectiveness'. |
| **Efficacy** | See 'Clinical efficacy'. |
| **Elective** | Name for clinical procedures that are regarded as advantageous to the patient but not urgent. |
| **Electrical stimulation** | Designed to increase venous blood flow velocity out of the leg to reduce the incidence of post-surgical venous thrombosis. |
| **Epidemiological study** | The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions. |
| **Equity** | Fair distribution of resources or benefits. |
| **Evidence** | Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients). |
| **Evidence table** | A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline. |
| **Exclusion criteria (literature review)** | Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence. |
| **Exclusion criteria (clinical study)** | Criteria that define who is not eligible to participate in a clinical study. |
| **Expert consensus** | See 'Consensus methods'. |
| **Extended dominance** | If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal. |
| **Extrapolation** | In data analysis, predicting the value of a parameter outside the range of observed values. |
| **Follow up** | Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables. |
| **Foot impulse device (FID)** | The foot impulse device is designed to stimulate the leg veins (venous pump) artificially by compressing the venous plexus and mimicking normal walking and reducing stasis in immobilised patients. |
| **Generalisability** | The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country. |
| **Gold standard** | See 'Reference standard'. |
| **Goodness-of-fit** | How well a statistical model or distribution compares with the observed data. |

| | |
|---|---|
| **Graduated compression stockings** | Sometimes known as anti-embolism stockings. Stockings manufactured to provide compression around legs at gradually increasing pressures. There are two different standards for graduated compression stockings, the British Standard and the European Standard (see Table 5). |
| **Grey literature** | Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems. |
| **Harms** | Adverse effects of an intervention. |
| **Health economics** | The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health. |
| **Health-related quality of life** | A combination of an individual's physical, mental and social well-being; not merely the absence of disease. |
| **Heparin-induced thrombocytopenia** | Low blood platelet count resulting from the administration of heparin (or heparin-like agents). Despite having a low platelet count, patients with this condition are at high risk of their blood clotting. |
| **Heterogeneity** | Or lack of *homogeneity*. The term is used in *meta-analyses* and *systematic reviews* when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up. |
| **HIT** | See 'Heparin-induced thrombocytopenia'. |
| **Homogeneity** | This means that the results of studies included in a *systematic review* or *meta-analysis* are similar and there is no evidence of *heterogeneity*. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. |
| **Hypothesis** | A supposition made as a starting point for further investigation. |
| **Inclusion criteria (literature review)** | Explicit criteria used to decide which studies should be considered as potential sources of evidence. |
| **Incremental analysis** | The analysis of additional costs and additional clinical outcomes with different interventions. |
| **Incremental cost** | The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention |
| **Incremental cost effectiveness ratio (ICER)** | The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest. |
| **Incremental net benefit (INB)** | The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost |
| **Index** | In epidemiology and related sciences, this word usually means a rating scale, for example, a set of numbers derived from a series of observations of specified variables. Examples include the various health status indices, and scoring systems for severity or stage of cancer. |
| **Indication (specific)** | The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA). |
| **Intention-to-treat analysis (ITT analysis)** | An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention. |
| **Intermediate outcomes** | Outcomes that are related to the outcome of interest but may be more easily |

| | |
|---|---|
| | assessed within the context of a clinical study: for example, blood pressure reduction is related to the risk of a stroke. |
| **Intermittent pneumatic compression (IPC)** | A method of prophylaxis that comprises the use of inflatable garments wrapped around the legs, inflated by a pneumatic pump. The pump provides intermittent cycles of compressed air which alternately inflates and deflates the chamber garments, enhancing venous return. |
| **Internal validity** | The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study's findings. See 'External validity'. |
| **Intervention** | Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy. |
| **Intraoperative** | The period of time during a surgical procedure. |
| **Length of stay** | The total number of days a participant stays in hospital. |
| **Licence** | See 'Product licence'. |
| **Life year** | A measure of health outcome which shows the number of years of remaining life expectancy. |
| **Life-years gained** | Average years of life gained per person as a result of the intervention. |
| **Mechanical** | Physical (as opposed to chemical) agent used, in this context, to reduce likelihood of thrombosis. |
| **Medical devices** | All products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or handicap. |
| **Medicines and Healthcare Products Regulatory Agency (MHRA)** | The Executive Agency of the Department of Health protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely. |
| **Meta-analysis** | A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials. |
| **Multivariate model** | A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable. |
| **Narrative summary** | Summary of findings given as a written description. |
| **Number needed to treat (NNT)** | The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest. |
| **Observational study** | Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies. |
| **Odds ratio** | A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events. |
| **Off-label** | A drug or device used treat a condition or disease for which it is not specifically licensed. |
| **Older people** | People over the age of 65 years. |
| **Operating costs** | Ongoing costs of carrying out an intervention, excluding capital costs. |
| **Opportunity cost** | The opportunity cost of investing in a healthcare intervention is the loss of other |

| | |
|---|---|
| | healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention. |
| **Outcome** | Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'. |
| **P values** | The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'. |
| **PE** | See 'Pulmonary embolism'. |
| **Peer review** | A process where research is scrutinised by experts that have not been involved in the design or execution of the studies. |
| **Perioperative** | The period from admission through surgery until discharge, encompassing pre-operative and post-operative periods. |
| **Placebo** | An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials. |
| **Placebo effect** | A beneficial (or adverse) effect produced by a *placebo* and not due to any property of the *placebo* itself. |
| **Post-thrombotic (Post-phlebitic) Syndrome** | Chronic pain, swelling, and occasional ulceration of the skin of the leg that occur as a consequence of previous venous thrombosis. |
| **Postoperative** | Pertaining to the period after patients leave the operating theatre, following surgery. |
| **Preoperative** | Pertaining to the period before surgery commences. |
| **Primary care** | Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians. |
| **Primary research** | Study generating original data rather than analysing data from existing studies (which is called secondary research). |
| **Product licence** | An authorisation from the MHRA to market a medicinal product. |
| **Prognosis** | A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes. |
| **Prophylaxis** | A measure taken for the prevention of a disease. |
| **Prospective study** | A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are *retrospective*. |
| **Proximal** | Refers to a part of the body that is closer to the centre of the body than another part. |
| **Pulmonary embolism (PE)** | A blood clot that breaks off from the deep veins and travels round the circulation to block the pulmonary arteries (arteries in the lung). Most deaths arising from DVT are caused by PE. |
| **Qualitative research** | Research concerned with subjective outcomes relating to social, emotional and experiential phenomena in health and social care. |
| **Quality of life** | See 'Health-related quality of life'. |
| **Quality-adjusted life-** | An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity |

| | |
|---|---|
| **year (QALY)** | (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment. |
| **Quantitative research** | Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households. |
| **Quick Reference Guide** | An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience. |
| **Randomisation** | Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias. |
| **Randomised controlled trial (RCT)** | A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups. |
| **RCT** | See 'Randomised controlled trial'. |
| **Relative risk (RR)** | The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B). |
| **Remit** | The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address. |
| **Resource implication** | The likely impact in terms of finance, workforce or other NHS resources. |
| **Retrospective study** | A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are *prospective*. |
| **Review of the literature** | An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed. |
| **Secondary benefits** | Benefits resulting from a treatment in addition to the primary, intended outcome. |
| **Selection bias (also allocation bias)** | A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias. |
| **Selection criteria** | Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence. |
| **Sensitivity (of a search)** | The proportion of relevant studies identified by a search strategy expressed as a percentage of all relevant studies on a given topic. It describes the comprehensiveness of a search method (that is, its ability to identify all relevant studies on a given topic). Highly sensitive strategies tend to have low levels of specificity and vice versa. |
| **Sensitivity analysis** | A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.<br>One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.<br>Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.<br>Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.<br>Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation). |

| | |
|---|---|
| **Stakeholder** | Those with an interest in the use of a technology under appraisal or a guideline under development. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups. |
| **Statistical power** | The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed. |
| **Synthesis of evidence** | A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries. |
| **Systematic review** | Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis. |
| **Thrombophilia** | The genetic or acquired prothrombotic states that increase the tendency to venous thromboembolism. It is a condition which leads to a tendency for a person's blood to clot inappropriately. |
| **Thromboprophylaxis** | A measure taken to reduce the risk of thrombosis. |
| **Time horizon** | The time span used in the NICE appraisal which reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence. |
| **Treatment allocation** | Assigning a participant to a particular arm of the trial. |
| **Treatment options** | The choices of intervention available. |
| **Utility** | A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value. |
| **Venous thromboembolism (VTE)** | The blocking of a blood vessel by a blood clot dislodged from its site of origin. It includes both DVT and PE. |
| **Venous thrombosis (VT)** | A condition in which a blood clot (thrombus) forms in a vein. |

# 1 Introduction

## 1.1 The need for this guideline

Venous thromboembolism (VTE) is the forming of a blood clot in a vein (venous thrombosis) which may dislodge from its site of origin. Each year there are a total of 25,000 deaths due to venous thromboembolism in England[246] (including medical and surgical patients). Most thrombi (clots) occur in the deep veins of the legs and this is called deep vein thrombosis (DVT). Dislodged thrombi may travel to the lungs and this is called a pulmonary embolus (PE). Formation is associated with inactivity and certain surgical procedures. The risk rises with the duration of operation and period of immobility.

DVT occurs in more than 20% of patients having major surgery and more than 40% of patients having major orthopaedic surgery. It is commonly asymptomatic. However, the condition can lead to sudden death due to PE, or cause long-term morbidity due to venous insufficiency and post-thrombotic syndrome (PTS), potentially leading to venous ulceration. With over 130,000 total hip replacements, total knee replacements, and femoral neck fractures annually[134] the personal and economic costs of venous thromboembolism in patients undergoing orthopaedic and other types of surgery are significant.

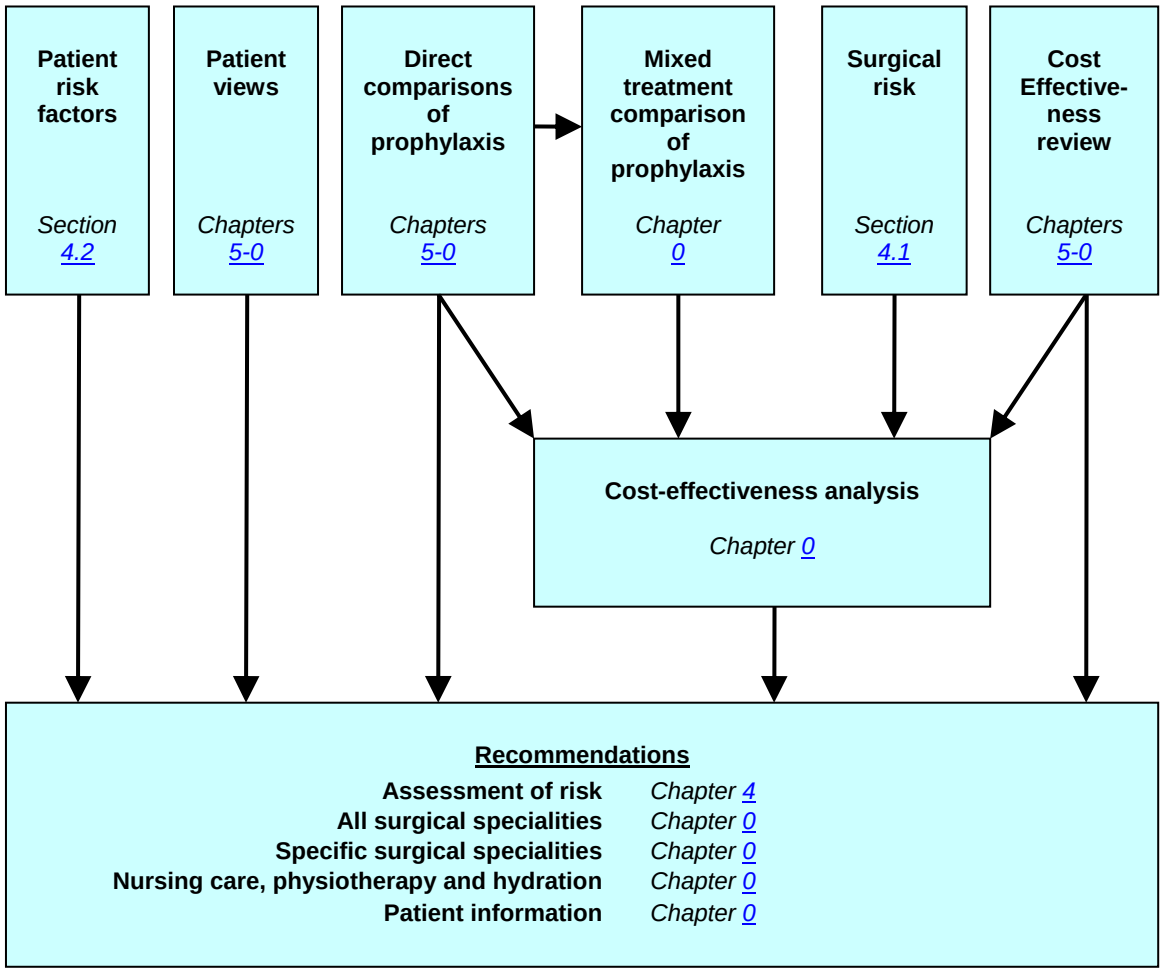
We have estimated that the risk of pulmonary embolism following high-risk surgery to be up to 5% in the highest risk groups (Chapter 4).

Current preventative measures available for patients undergoing surgical procedures include mechanical/physical prophylaxis (such as graduated elastic compression stockings, foot impulse devices and intermittent pneumatic compression) and pharmaceutical prophylaxis. Wide variation of clinical practice and non observance with previous clinical guidelines[85,276] suggest that many patients are currently not receiving adequate prophylactic measures.

This guideline examines the risk of venous thromboembolism and assesses the evidence for the effectiveness of preventative measures. It provides recommendations on the most clinically and cost effective measures to reduce the risk of venous thromboembolism in surgical inpatients, whilst considering potential adverse effects of the various preventative options and patient preferences.

We start by examining the risk factors for developing VTE (both surgical related and patient related), followed by a detailed review of the evidence of clinical and cost effectiveness for each of the preventative methods that we are considering. We then describe the results of a combined meta-analysis that brings these studies together and allows comparisons to be made across methods. We continue by describing the results of our cost effectiveness analysis and conclude by examining how these results can be interpreted for different surgical specialties. The path from evidence to recommendations is illustrated further in the next section.

### 1.1.1 Summary of the path from evidence to recommendations in this guideline




## 1.2 Assumptions made in this guideline

This guideline recommends prophylaxis on the basis of effectiveness in reducing the risk of DVT (both symptomatic and asymptomatic), acknowledging that this is a 'surrogate' endpoint which is frequently employed in randomised controlled trials (RCTs).

There are several difficulties with considering only pulmonary embolism (PE) as an outcome. Firstly, PE is a rare event, and therefore large trials (or numbers of trials) are needed to demonstrate an effect. Secondly, few trials that report PE have made the diagnosis using objective methods (clinical diagnosis being unreliable).Thirdly, many trials that report PE as an outcome measure have also assessed all included patients for DVT. Trial protocols usually dictate that patients in whom a DVT is detected are removed from the trial and anticoagulation is given, and hence a PE may be prevented that would have occurred in the usual clinical setting.

DVT is a usual precursor of both fatal PE and post-thrombotic syndrome (PTS), although the aetiology and development of the diseases have not yet been fully elucidated. Although asymptomatic DVT is, by definition, covert these thrombi can become pulmonary embolisms and are a clinically useful endpoint for a trial. We therefore consider it appropriate to evaluate both asymptomatic and symptomatic DVT when looking at the effectiveness of prophylactic strategies. Clinical detection of DVT is unreliable and also fails to detect asymptomatic events, hence we have only included trials that assess all patients for DVT using objective methods.

DVT, therefore, is accepted as a suitable endpoint by this guideline which will evaluate trials where patients are assessed for DVT.

## 1.3 What are clinical practice guidelines?

Our clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care though primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific clinical questions.

Clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Collaborating Centre for Acute Care (NCC-AC)
- The National Collaborating Centre for Acute Care establish a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The National Collaborating Centre for Acute Care and NICE produce a number of versions of this guideline:

- the full guideline contains all the recommendations, plus details of the methods used and the underpinning evidence
- the NICE guideline presents the recommendations from the full version in a format suited to implementation by health professionals and NHS bodies
- the quick reference guide presents recommendations in a suitable format for health professionals
- information for the public ('understanding NICE guidance') is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from the NCC-AC website at www.rcseng.ac.uk/surgical_research_units/nccac/ or are available from NICE www.NICE.org.uk.

## 1.4 The National Collaborating Centre for Acute Care

This guideline was commissioned by NICE and developed by the National Collaborating Centre for Acute Care. The centre is one of seven national collaborating centres funded by NICE and comprises a partnership between a variety of academic, professional and patient-based organisations. As a multidisciplinary centre we draw upon the expertise of the healthcare professions and academics and ensure the involvement of patients in our work. Further information on the centre and our partner organisations can be found at our website (www.rcseng.ac.uk/surgical_research_units/nccac/).

## 1.5 Remit of the Guideline

The following remit was received from the Department of Health and the Welsh Assembly Government in March 2003 as part of NICE's 8th wave programme of work.

"***To develop safety guidance for the NHS in England and Wales on prophylaxis against venous thromboembolism (VTE) for patients undergoing orthopaedic surgery and other surgical procedures for which there is a high risk of VTE. The guidance should set out the principles of clinical and cost effective practice and in particular should address:***

***i. the assessment of risk for particular procedures and for individual patients,***

***ii. the circumstances in which prophylaxis can be recommended as clinically and cost effective, and***

***iii. appropriate selection of interventions including both pharmaceutical and mechanical methods of prophylaxis."***

## 1.6 What the guideline covers

This guideline covers adults (age 18 and older) undergoing inpatient surgical procedures that carry a high risk of venous thromboembolism, including:

- orthopaedic surgery (for example, total hip or knee replacement, surgery for hip fracture)
- major general surgery
- major gynaecological surgery (but not elective or emergency caesarean)
- urological surgery (including major or open urological procedures)
- neurosurgery
- cardiothoracic surgery
- major peripheral vascular surgery.

The scope for this guideline can be found in Appendix A.

## 1.7 What the guideline does not cover

This guideline does not cover patients under the age of 18.

Additionally this guideline does not cover adult patients who are at a high risk of developing venous thromboembolism but are not undergoing surgery. For example the following circumstances and patients are excluded from the guideline (unless patients are undergoing one of the surgical procedures listed above):

- patients with acute myocardial infarction
- patients who have had an acute stroke
- patients with cancer, including those being treated with chemotherapy
- pregnancy and the puerperium
- use of oral contraceptives and hormone replacement therapy
- long-distance travel.

## 1.8 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Collaborating Centre for Acute Care (NCC-AC) and thus supported the development of this guideline. The GDG was convened by the NCC-AC and chaired by Professor Tom Treasure in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every 6-8 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B). Members are either required to withdraw completely or for part of the discussion if their declared interest makes it appropriate, however this was not deemed necessary for any group members on this guideline.

Staff from the NCC-AC provided methodological support and guidance for the development process. They undertook systematic searches, retrieval and appraisal of the evidence and drafted the guideline. The glossary to the guideline contains definitions of terms used by staff and the GDG.

# 2 Summary of Recommendations

Below are the recommendations that the GDG selected as the key priorities for implementation followed by the full list of recommendations.

## 2.1 Key Priorities for Implementation

- Patients should be assessed to identify their risk factors for developing VTE (see box 1, section 2.2.1).
- Healthcare professionals should give patients verbal and written information, before surgery, about the risks of VTE and the effectiveness of prophylaxis.
- Inpatients having surgery should be offered thigh-length graduated compression/anti-embolism stockings from the time of admission to hospital unless contraindicated (for example, in patients with established peripheral arterial disease or diabetic neuropathy). If thigh-length stockings are inappropriate for a particular patient for reasons of compliance or fit, knee-length stockings may be used as a suitable alternative.
- The stocking compression profile should be equivalent to the Sigel profile, and approximately 18 mmHg at the ankle, 14 mmHg at the mid-calf and 8 mmHg at the upper thigh.
- Patients using graduated compression/anti-embolism stockings should be shown how to wear them correctly by healthcare professionals trained in the use of that product. Stocking use should be monitored and assistance provided if they are not being worn correctly.
- Intermittent pneumatic compression or foot impulse devices may be used as alternatives or in addition to graduated compression/anti-embolism stockings while surgical patients are in hospital.
- In addition to mechanical prophylaxis, patients at increased risk of VTE because they have individual risk factors (see box 1) and patients having orthopaedic surgery should be offered low molecular weight heparin (LMWH). Fondaparinux, within its licensed indications, may be used as an alternative to LMWH.
- Low molecular weight heparin or Fondaparinux should be continued for 4 weeks after hip fracture surgery.
- Regional anaesthesia reduces the risk of VTE compared with general anaesthesia. Its suitability for an individual patient and procedure should be considered, along with the patient's preferences, in addition to any other planned method of thromboprophylaxis.
- Healthcare professionals should encourage patients to mobilise as soon as possible after surgery.

## 2.2 The complete list of clinical practice recommendations

### 2.2.1 Assessment of risk and patient advice

**Box 1: Patient-related risk factors for venous thromboembolism**

- Active cancer or cancer treatment
- Active heart or respiratory failure
- Acute medical illness
- Age over 60 years
- Antiphospholipid syndrome
- Behcet's disease
- Central venous catheter in situ
- Continuous travel of more than 3hours approximately 4weeks before or after surgery
- Immobility (for example, paralysis or limb in plaster)
- Inflammatory bowel disease (for example Crohn's disease or ulcerative colitis)
- Myeloproliferative diseases
- Nephrotic syndrome
- Obesity (body mass index $\geq 30 kg/m^2$)
- Paraproteinaemia
- Paroxysmal nocturnal haemoglobinuria
- Personal or family history of VTE
- Pregnancy or puerperium
- Recent myocardial infarction or stroke
- Severe infection
- Use of oral contraceptives or hormonal replacement therapy
- Varicose veins with associated phlebitis
- Inherited Thrombophilias for example:
  - High levels of coagulation factors (for example, Factor VIII)
  - Hyperhomocysteinaemia
  - Low activated protein C resistance (for example, Factor V Leiden)
  - Protein C, S and antithrombin deficiencies
  - Prothrombin 2021A gene mutation

- Patients should be assessed to identify their risk factors for developing venous thromboembolism (VTE; see Box 1)

- Healthcare professionals should give patients verbal and written information, before surgery, about the risks of VTE and the effectiveness of prophylaxis.

- Healthcare professionals should inform patients that the immobility associated with continuous travel of more than 3 hours in the 4 weeks before or after surgery may increase the risk of VTE.

- Healthcare professionals should advise patients to consider stopping combined oral contraceptive use 4 weeks before elective surgery [see Royal College of Obstetricians and Gynaecologists guideline no. 40][450].

- Healthcare professionals should give patients verbal and written information on the following, as part of their discharge plan.
  - The signs and symptoms of DVT and PE.
  - The correct use of prophylaxis at home.
  - The implications of not using the prophylaxis correctly.

### 2.2.2 Reducing the risk of venous thromboembolism in all surgical specialities

- Inpatients having surgery should be offered thigh-length graduated compression/anti-embolism stockings from the time of admission to hospital unless contraindicated (for example, in patients with established peripheral arterial disease or diabetic neuropathy) .If thigh length stockings are inappropriate for a particular patient for reasons of

compliance or fit, knee-length stockings may be used as a suitable alternative.

- The stocking compression profile should be equivalent to the Sigel profile, and approximately 18 mmHg at the ankle, 14 mmHg at the mid-calf and 8 mmHg at the upper thigh.

- In addition to mechanical prophylaxis, patients at increased risk of VTE because they have individual risk factors (see box 1) and patients having orthopaedic surgery should be offered low molecular weight heparin (LMWH). Fondaparinux, within its licensed indications, may be used as an alternative to LMWH.

- Healthcare professionals should encourage patients to wear their graduated compression/anti-embolism stockings until they return to their usual level of mobility. Patients should be informed that this will reduce their risk of developing VTE.

- Patients using graduated compression/anti-embolism stockings should be shown how to wear them correctly by healthcare professionals trained in the use of that product. Stocking use should be monitored and assistance provided if they are not being worn correctly.

- Intermittent pneumatic compression or foot impulse devices may be used as alternatives or in addition to graduated compression/anti-embolism stockings while surgical patients are in hospital.

- When used on the ward, intermittent pneumatic compression or foot impulse devices should be used for as much of the time as is possible and practical while the patient is in bed or sitting in a chair.

- Vena caval filters should be considered for surgical inpatients with recent (within 1 month) or existing VTE and in whom anticoagulation is contraindicated.

- The risks and benefits of stopping pre-existing established anticoagulation or antiplatelet therapy before surgery should be considered.

- Regional anaesthesia reduces the risk of VTE compared with general anaesthesia. Its suitability for an individual patient and procedure should be considered, along with the patient's preferences, in addition to any other planned method of thromboprophylaxis.

- If a regional anaesthetic technique is used, the timing of pharmacological prophylaxis should be carefully planned to minimise the risk of haematoma.

- Healthcare professionals should not allow patients having surgery to become dehydrated during their stay in hospital.

- Healthcare professionals should encourage patients to mobilise as soon as possible after surgery.

- Healthcare professionals should arrange for immobilised patients to have leg exercises.

### 2.2.3 Reducing the risk of venous thromboembolism by type of surgery

There may be other surgical procedures requiring an inpatient stay that are not covered in this guideline. Healthcare professionals should exercise their clinical judgement when making decisions on the appropriateness of VTE prophylaxis.

Please see the summary of product characteristics for details on the timing and administration of pharmacological prophylaxis.

#### 2.2.3.1 Orthopaedic Surgery (spinal surgery considered with neurosurgery)

*Elective orthopaedic surgery*

- Patients having elective orthopaedic surgery should be offered mechanical prophylaxis and either LMWH or fondaparinux.

- Patients having hip replacement surgery with one or more risk factors for VTE (see box 1) should have their LMWH or fondaparinux therapy continued for 4 weeks after surgery.

*Hip fracture surgery*

- Patients having surgery for hip fracture should be offered mechanical prophylaxis and either LMWH or fondaparinux.

- LMWH or Fondaparinux therapy should be continued for 4 weeks after hip fracture surgery.

#### 2.2.3.2 General surgery recommendations

- Patients having general surgery should be offered mechanical prophylaxis.

- Patients having general surgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and either LMWH or fondaparinux.

#### 2.2.3.3 Gynaecological surgery recommendations (excluding caesarean section)

- Patients having gynaecological surgery should be offered mechanical prophylaxis.
- Patients having gynaecological surgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LWMH.

#### 2.2.3.4 Cardiac surgery recommendations

- Patients having cardiac surgery should be offered mechanical prophylaxis.
- Patients having cardiac surgery who are not otherwise receiving anticoagulation therapy and who have one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LMWH.

#### 2.2.3.5 Thoracic surgery recommendations

- Patients having thoracic surgery should be offered mechanical prophylaxis.
- Patients having thoracic surgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LMWH.

#### 2.2.3.6 Urological surgery recommendations

- Patients having urological surgery should be offered mechanical prophylaxis.
- Patients having urological surgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LMWH.

#### 2.2.3.7 Neurosurgery (including spinal surgery) recommendations

- Patients having neurosurgery should be offered mechanical prophylaxis.
- Patients having neurosurgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LMWH.
- Patients with ruptured cranial or spinal vascular malformations (for example, brain aneurysms) should not be offered pharmacological prophylaxis until the lesion has been secured.

#### 2.2.3.8 Vascular surgery recommendations

- Patients having vascular surgery should be offered mechanical prophylaxis.
- Patients having vascular surgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LMWH.

## 2.3 Recommendations summary table

| Surgical speciality (Excludes day case surgery) | No patient related risk factors | One or more patient related risk factor |
|---|---|---|
| **Elective Hip Replacement** | Mechanical + LMWH/ Fond | Mechanical + LMWH/ Fond continued for 4 weeks |
| **Hip Fracture** | Mechanical + LMWH/ Fond continued for 4 weeks | Mechanical + LMWH/ Fond continued for 4 weeks |
| **Other Orthopaedic** | Mechanical + LMWH/ Fond | Mechanical + LMWH/ Fond |
| **General** | Mechanical | Mechanical + LMWH/ Fond |
| **Gynaecological** | Mechanical | Mechanical + LMWH |
| **Cardiac** | Mechanical | Mechanical + LMWH * |
| **Thoracic** | Mechanical | Mechanical + LMWH |
| **Urological** | Mechanical | Mechanical + LMWH |
| **Neurosurgery** | Mechanical | Mechanical + LMWH** |
| **Vascular** | Mechanical | Mechanical + LMWH |

Fond= fondaparinux, LMWH= low molecular weight heparin, *= if not otherwise anticoagulated, ** except patients with ruptured cranial or spinal vascular malformations if the lesion has not been secured, Mechanical = graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices.

## 2.4 Recommendations for research

The GDG identified the following priority areas for research.

### 2.4.1 Incidence of clinical DVT, confirmed PE, major bleeding, and other postoperative adverse outcomes in modern surgical practice.

#### 2.4.1.1 Research Question

What is the relevance of surgical procedure and patient risk factors to incidence of clinical DVT, confirmed PE, major bleeding, and other postoperative adverse outcomes (e.g. myocardial infarction, stroke) in modern surgical practice?

The aim should be to recruit patients undergoing a range of surgical procedures with different levels of expected risk of VTE, ensuring coverage of the common operations currently performed in the NHS.

Baseline evaluation would aim to identify risk factors for VTE and for other adverse outcomes (e.g. bleeding and occlusive vascular events). The study would also record any in-hospital drug treatment and discharge medication. Note, however, that this would be a large observational cohort study and would not be appropriate for determining the effects of treatment, since moderate effects cannot be assessed reliably by such studies.

The control (reference) group will be defined, for each parameter (e.g. age) by a category of patients at low risk of VTE (e.g. age < 30).

#### 2.4.1.2 Why this research is important

The chief difficulty faced when formulating the present guideline was the absence of accurate estimates of VTE risk in the modern era. Although it was possible to estimate the relative risk reductions associated with particular interventions, it was not possible to estimate their associated absolute benefits. It is possible that the modern risks of VTE are much lower than is represented by the available trial evidence. Information on absolute risks of VTE (and other postoperative complications) needs to be obtained in order to assess cost effectiveness reliably.

Information from this study would help surgical teams to provide their patients with accurate information about the balance of benefit and risk associated with particular interventions.

This study could be performed easily if the design elements were kept simple, with one-sided forms

that could be completed at discharge, and follow-up through mailed questionnaires and tracking of mortality via the Office of National Statistics.

### 2.4.2 Timing of administration of low molecular weight heparin

#### 2.4.2.1 Research Question

What is the effectiveness of LMWH started pre-operatively compared to LMWH started post-operatively in reducing the risk of (objectively diagnosed) DVT or PE in adult patients undergoing inpatient surgical procedures?

All patients should be screened for the presence of DVT and/or PE. Secondary outcomes of interest are costs, quality of life, other adverse events (e.g. myocardial infarction, stroke, extracranial or intracranial bleeding).

#### 2.4.2.2 Why this research is important

The currently available randomised evidence is too limited to determine whether giving LMWH can be safely delayed until after surgery, or whether it must be given pre-operatively. This guideline recommends that LMWH is used for many patients at risk of VTE and is therefore non-specific about timing. This is a major gap in the evidence.

Although there may be only small differences in safety and efficacy between these two strategies, a policy of giving LMWH post-operatively may reduce the time that patients need to be in hospital before surgery and therefore have major benefits for patients.

As there is uncertainty around this question, it should be possible to find surgeons willing to randomise between these two strategies. The principal practical difficulty with this randomised trial would be the need for a very large sample size (with possibly more than 10,000 patients), because the likely differences in DVT/PE and bleeding rates are small.

### 2.4.3 The effectiveness of combining methods of mechanical prophylaxis

#### 2.4.3.1 Research Question

What is the effectiveness of graduated compression/anti-embolism stockings and either an intermittent pneumatic compression (IPC) device or a foot pump, device compared with graduated compression/anti-embolism stockings alone, in reducing the risk of (objectively diagnosed) DVT and/or PE in adult inpatients undergoing surgery? Patients may be high risk of VTE because of the procedure (e.g. hip fracture), or because they have risk factors for such disease (e.g. thrombophilia, age over 60 years).

All patients should be screened for the presence of DVT and/or PE.

Randomisation would be stratified into two groups:

- Patients in whom pharmacological prophylaxis is contraindicated (e.g. because of an increased risk of bleeding).

- Patients in whom pharmacological prophylaxis is indicated, but the risk of VTE is very high.

Secondary outcomes would be costs, quality of life, skin problems, myocardial infarction, stroke and other adverse events e.g. bleeding,

#### 2.4.3.2 Why this research is important

Only a small number of RCTs have evaluated a combination of mechanical methods. These studies have shown promising results, but have involved small numbers of patients and the large effect sizes observed in some of these studies suggest bias.

This trial would inform the management of two specific groups of patients in whom the available treatment options are restricted.

- Patients at high risk of VTE who cannot have LMWH because they are at increased risk of bleeding.

- Patients at very high risk of VTE who can be given pharmacological prophylaxis who might benefit from combination mechanical thromboprophylaxis.

This trial would help extend the current NICE recommendations. There may be cost savings if the addition of a second mechanical method results in further risk reduction of VTE.

The proposed research is feasible but depends on the extent to which surgeons are certain about the value of combining two mechanical methods of thromboprophylaxis, because this would determine their willingness to randomise. Before any trial this issue would need to be explored in detail, possibly via a questionnaire.

# 3 Methodology

## 3.1 Guideline methodology

The guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in 'The guidelines manual' updated in April 2006[389]. Development prior to this stage (e.g. development of the scope, early reviewing) was carried out using the methodology outlined in the previous version of the manual (March 2005).

## 3.2 Developing the clinical questions

Clinical questions were developed to guide the literature searching process and to facilitate the development of recommendations by the guideline development group.

The clinical questions were initially drafted by the review team and were refined and validated by the guideline development group. The questions were based on the scope (Appendix A). Further information on the outcome measures we examined follows this section.

### 3.2.1 Questions on effectiveness of interventions to reduce the risk of post-operative venous thromboembolism (VTE)

We considered the effectiveness of the following interventions:

a) Graduated elastic compression stockings (GCS)

b) Intermittent pneumatic compression (IPC) devices

c) Foot pumps or foot impulse devices (FID)

d) Electrical stimulation

e) Vena caval filters

f) Aspirin or antiplatelet therapy

g) Low-dose unfractionated heparin administered subcutaneously (UFH)

h) Low molecular weight heparin (LMWH)

i) The synthetic pentasaccharide, Fondaparinux

j) Oral anticoagulants (For example, warfarin, coumarin)

k) Dextrans

l) Early mobilisation

m) Foot elevation

n) Hydration

o) Placebo or no intervention

The clinical question was:

- *What is the effectiveness of X vs Y in reducing the incidence of VTE*

(where X and Y are selected from the list of interventions above). Every possible combination was compared.

The effectiveness of combinations of methods of prophylaxis (For example, a combination of a mechanical and a pharmacological intervention or two mechanical devices) were also considered versus no prophylaxis, versus single methods or versus other combinations.

### 3.2.2 Additional considerations on the use of the above interventions

We examined more detailed aspects of the use of some of the interventions above.

- Potential variations in effectiveness by dose (for Dextrans, OAC and LMWH)
- The timing of administration of pharmacological prophylaxis (for OAC and LMWH)
- Extending pharmacological prophylaxis beyond the hospitalised period (for OAC, LMWH and fondaparinux)

- The length of compression stocking (knee length vs. over the knee)

### 3.2.3 Anaesthesia

The questions we examined were:

- *What is the effectiveness of regional anaesthesia vs general anaesthesia in reducing the incidence of postoperative VTE?*
- *Does adding a regional to a general anaesthetic reduce the risk of postoperative VTE?*

### 3.2.4 Risk Factors

We developed questions to address risk factors for VTE associated with surgical procedure and for individuals:

- *Which surgical procedures carry a high risk of DVT/PE?*
- *Which individual patient factors are risk factors for developing DVT/PE?*

### 3.2.5 Patient Information and Communication

We examined the following clinical question:

- *What is the effectiveness of providing patients with information on reducing the risk of postoperative VTE vs standard care in reducing the incidence of postoperative VTE*

### 3.2.6 Patient Views and Preferences

We searched for evidence of patient preferences regarding all the interventions listed above.

## 3.3 Patient groups covered by this guideline

We searched for studies of adults (age 18 years and older) undergoing surgical procedures as inpatients, including: orthopaedic surgery; general surgery; gynaecological surgery (but not elective or emergency Caesarean); urological surgery; neurosurgery; cardiothoracic surgery; and peripheral vascular surgery. A more detailed list of patient groups that are included or excluded from the guideline can be found in the scope (Appendix A).

## 3.4 Outcomes

### 3.4.1 Primary Outcomes

The following primary outcomes were included:

#### 3.4.1.1 Deep-vein thrombosis (DVT)

DVT (symptomatic and asymptomatic) identified by one of the following methods:

- Radioiodine ($^{125}$I) fibrinogen uptake
- Venography
- Doppler ultrasound
- Magnetic resonance imaging (MRI)

In order to detect all asymptomatic DVTs our inclusion criteria for this outcome required that **all** patients included in the study were screened using one or more of the methods outlined. Studies that only assessed patients with clinical suspicion of DVT were not included for this outcome.

The following methods of diagnosing DVT were excluded as they were considered to be unreliable (unless used in conjunction with one of the methods outlined above):

- D-dimer blood assay test
- Impedance plethysmography
- Clinical examination alone

#### 3.4.1.2 Proximal DVT

Proximal DVT (symptomatic and asymptomatic), defined as deep vein thrombosis involving the veins above the knee, and determined by the methods outlined for deep vein thrombosis.

#### 3.4.1.3 Pulmonary embolism (PE)

PE (asymptomatic, symptomatic or fatal), determined by one or more of the following methods

- Pulmonary angiogram
- Ventilation/perfusion scan (pulmonary scintigraphy)
- CT pulmonary angiogram (CTPA)
- Autopsy

•Clinical suspicion confirmed by one of the preceding methods

The following methods of diagnosing PE were excluded as they were considered to be unreliable:

•Chest X-ray alone

•Clinical diagnosis alone

#### 3.4.1.4 Major bleeding events

Bleeding events were considered to be "major" on the basis of the authors' own established criteria, or if the results reported corresponded to the following definitions:

•results in death,

•decrease in haemoglobin concentration of 2g/dl or more

•transfusion of at least 2 units of blood

•if it was retroperitoneal, intracranial, or intraocular

•if it resulted in a serious or life-threatening clinical event

• or if surgical or medical intervention was required.

### 3.4.2 Secondary Outcomes

The following secondary outcomes were also included in our review where reported:

- post-thrombotic syndrome (PTS)
- heparin-induced thrombocytopenia (HIT)
- neurological events
- quality of life
- survival
- length of stay.

### 3.4.3 Important methodological issues relating to the outcomes

• Pulmonary emboli, major bleeds, spinal haematomas and heparin-induced thrombocytopenia are rare events; consequently, large numbers of patients are required to obtain an estimate of effect.

• Very few trials assess all patients for pulmonary embolism using objective methods.

• Where trials assess both DVT and pulmonary embolism, protocols usually dictate that patients in whom a DVT is detected are withdrawn and started on anticoagulant therapy which may prevent further progression of the disease. This may result in an underestimation of the PE rate as many of these patients (particularly those with asymptomatic DVT) would not have been picked up in standard practice.

• The estimates of effect on proximal DVT may be susceptible to bias because a decision to report this outcome in trial publications could have been influenced by the direction or the size of the findings.

• Very few trials reported any of the secondary outcomes.

## 3.5 Clinical literature search

The aim of the literature search was to identify relevant evidence within the published literature, in order to answer the clinical questions identified. Searches of clinical databases were performed using generic and specific filters, relevant medical subject heading terms and free-text terms. Non-English studies and abstracts were not included. Each database was searched up to 7 August 2006. Papers identified after this date were not considered. Search strategies can be found in appendix C. The following databases were included in the literature search to identify relevant journal articles:

•The Cochrane Library up to 2006 (Issue 2)

•Medline (Dialog Datastar) 1951-2006

•Embase (Dialog Datastar) 1974-2006

•Cinahl (Dialog Datastar) 1982-2006

Bibliographies of identified reports and guidelines were also checked to identify relevant literature. The Internet was searched to identify guidelines and reports. The following web sites were used to help identify these:

• Members of the Guidelines International Network's web sites (http://www.g-i-n.net/ )

• National Institute of Health and Clinical Excellence (NICE) (www.nice.org.uk)

- National electronic Library for Health (NeLH) (http://www.nelh.nhs.uk/)
- National Institutes of Health Consensus Development Program (consensus.nih.gov)
- New Zealand Guidelines Development Group (NZGG) (http://www.nzgg.org.nz/)
- Scottish Intercollegiate Guideline Network (SIGN) (www.sign.ac.uk)
- US National Guideline Clearing House (www.guidelines.gov)

Table 1.

For each clinical question the highest level of evidence was sought. Where an appropriate systematic review, meta-analysis or randomised controlled trial was identified, we did not search for studies of a weaker design.

### 3.6 Hierarchy of clinical evidence

There are many different methods of ranking the evidence and there has been considerable debate about which system is best. We used the system, developed by the Scottish Intercollegiate Guidelines Network (SIGN), shown

**Table 1: Levels of evidence for intervention studies (reproduced with permission of the Scottish Intercollegiate Guidelines Network)**

| Level of evidence | Type of evidence |
|---|---|
| 1++ | High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias |
| 1+ | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias |
| 1- | Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias |
| 2++ | High-quality systematic reviews of case–control or cohort studies<br>High-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal |
| 2+ | Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal |
| 2- | Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal |
| 3 | Non-analytic studies (For example, case reports, case series) |
| 4 | Expert opinion, formal consensus |

## 3.7 The literature reviewing process

References identified by the systematic literature search were screened for appropriateness by title and abstract by an information scientist and systematic reviewer. Studies were selected that reported one or more VTE outcome (DVT, proximal DVT, pulmonary embolism) determined by objective/reliable methods. We did not select studies that reported only major bleeding outcomes, but where an included systematic review reported such studies, they were not removed. The guideline development group also suggested further references and we assessed these in the same way.

Selected studies were ordered and assessed in full by the NCC-AC team using agreed inclusion/ exclusion criteria specific to the guideline topic, and using NICE methodology quality assessment checklists appropriate to the study design[389].

## 3.8 Evidence submitted by stakeholders

Stakeholders were invited to submit potential evidence of relevance to the guideline. References received were cross-checked with evidence identified through the systematic literature search. Stakeholder-submitted references were assessed using the same criteria for inclusion as studies retrieved in the literature search.

## 3.9 Methods of combining studies – direct comparisons

Where possible, meta-analyses were conducted to combine the results of studies addressing the same clinical question using Cochrane's Review Manager software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) of an event occurring, that is, DVT, proximal DVT, PE or major bleeding. Heterogeneity was assessed by the Q statistic. A Q statistic with $p<0.05$ was taken to indicate significant heterogeneity. We carried out sensitivity analyses to identify studies whose results were heterogeneous to the overall result. Any such studies were further assessed to identify any clinical or methodological causes. We avoided removing these studies from the meta-analyses unless we identified a serious methodological flaw, as removal would introduce bias into the systematic review. Where no cause of statistical heterogeneity could be determined a random effects (DerSimonian and Laird) model was employed.

Subgroup analyses based on subsets of studies were carried out to address some clinical questions where there was insufficient direct evidence. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics, using the formula $Q_{int} = Q_{all} – (Q_1 + … + Q_m)$ where $Q_{int}$ represents the difference between subgroups, $Q_{all}$ is the heterogeneity of the overall unsubgrouped analysis, and $Q_1$ to $Q_m$ represent the heterogeneities of each subgroup, m being the total number of subgroups. $Q_{int}$ was compared with a chi-squared distribution with n-1 degrees of freedom to test for a difference between the subgroups[132].It is important to note that subgroup analyses of studies are observational and are not based on randomised comparisons, and therefore represent weaker evidence than direct comparisons made within RCTs. Where combining results of trials in a meta-analysis was not appropriate a narrative synthesis of studies was undertaken.

## 3.10 Subgroup analyses by type of surgery

Data was initially analysed by method of prophylaxis, that is, evidence from all surgery types was pooled to assess the overall effectiveness of interventions. Subgroup analyses were carried out to look for evidence of heterogeneity in the risk reductions between different types of surgery. Chi-squared tests for heterogeneity were carried out to identify comparisons where evidence of differences between surgical contexts was apparent. Subgroup analyses showing statistically significant differences were presented to the guideline development group to decide whether the findings indicated a clinically important difference.

## 3.11 Mixed-treatment comparisons analysis

It is difficult to determine the most effective prophylaxis strategy from the results of conventional meta-analyses of direct evidence (as presented in chapters 5 to 10) for two reasons:

- Some pairs of alternative strategies have not been directly compared in an RCT (For example, danaparoid vs fondaparinux)

- There are frequently multiple overlapping comparisons (For example, heparin vs no prophylaxis, heparin vs stockings and stockings vs no prophylaxis), that give inconsistent estimates of effect.

To overcome these problems, we conducted a mixed-treatment comparisons (MTC) meta-analysis that pools together all the data. This allowed us to rank the different prophylaxis interventions in order of efficacy at reducing DVTs and in order of risk of major bleeding. For each of these two outcomes It gives us a single estimate of effect (with confidence intervals) for each intervention. These estimates are essential to facilitate a cost-effectiveness analysis of different prophylaxis strategies.

The MTC analyses are used to compliment our analysis of direct comparison evidence. And therefore we have scrutinised the MTC analyses to ensure that they are consistent with the direct evidence.

Detailed methods are reported in chapter 12 and appendix F.

## 3.12 Health economics methods

It is important to investigate whether health services are clinically effective and also cost-effective (that is, value for money). If a particular prophylaxis or treatment strategywere found to yield little health gain relative to the resources used, then it would be advantageous to re-deploy resources to other activities that yield greater health gain.

To assess the cost-effectiveness of each recommendation, a comprehensive systematic review of the economic literature was conducted. In addition, an original cost-effectiveness analysis was performed which compared a variety of different prophylactic strategies for a number of different surgical scenarios.

The criteria applied for an intervention to be considered cost-effective were either:

a) The intervention dominated other relevant strategies (that is, it is both less costly in terms of resource use and more clinically effective compared with the other relevant alternative strategies)[1];

or

b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy (and compared with no prophylaxis). Where QALYs were not estimated, we used thresholds of £20,000 per life-year gained, or £400,000 per life saved.

[1] Where there was no overall measure of health gain reported, we have used the term 'dominant' to refer to a strategy that reduces VTEs and reduces cost. However, strictly speaking it ought to be an outcome that includes the impact of both VTEs and major bleeding.

We have stated that cost-effectiveness is 'indeterminable' in cases where outcomes are expressed only in terms of VTEs rather than overall health outcomes and where one intervention is both more costly and more effective.

The economic evaluation of any strategy has to be in comparison with another strategy. Hence we refer to:

- *incremental cost*: the mean cost of one strategy minus the mean cost of a comparator study
- *QALYs gained*: the mean QALYs associated one strategy minus the mean QALYs of a comparator study
- *incremental cost-effectiveness ratio*: the incremental cost divided by the respective QALYs gained
- *incremental net benefit (INB)*: the (monetary) value of a strategy compared with an alternative strategy for a given cost-effectiveness threshold (For example. £20,000 per QALY gained).

In our own cost-effectiveness analysis (Chapter 13), we use the following formula to estimate the INB of each strategy:

INB= (QALYs gained compared with no prophylaxis x £20,000) minus the incremental cost compared with no prophylaxis

This indicates that we will invest up to £20,000 to gain one additional QALY. The strategy that has the highest INB is the optimal (that is, most cost-effective) strategy. Strategies that have a negative INB are not cost-effective even compared with no prophylaxis.

### 3.12.1 Literature review for Health Economics

We obtained published economic evidence from a systematic search of the following databases:

- Medline (Dialog Datastar) (1966-2006)
- Embase (Dialog Datastar) (1980-2006)
- Health Economic Evaluations Database (HEED)
- NHS Economic Evaluations Database (NHS EED)

For those clinical areas we reviewed, the information specialists used the same search strategy as for the clinical questions, using an economics filter in the place of a systematic review or randomised controlled trial filter. Each database was searched from its start date up to 7 August

2006. Papers identified after this date were not considered. Search strategies can be found in Appendix C.

Each search strategy was designed to find any applied study estimating the cost or cost-effectiveness of an included prophylaxis intervention. A health economist reviewed the abstracts. Relevant references in the bibliographies of reviewed papers were also identified and reviewed.

Given the diversity of economic studies, it was not possible to determine a general exclusion criterion based on study quality. Hence, all studies were included in the evidence tables and study quality and applicability are discussed in the review. Papers were only excluded from the evidence tables and review if:

- The study did not contain any original data on cost or cost-effectiveness (that is, it was a review or a clinical paper).

- The analysis was not incremental and was not described adequately to allow incremental analysis (so studies reporting only average cost-effectiveness ratios were excluded unless they provided data to allow the calculation of incremental cost-effectiveness ratios).

- Cost analyses were excluded if the results were not presented in a way that would allow the incremental cost per patient to be extracted or derived.

Where a comparison had a large number of evaluations (For example, LMWH vs UFH), we excluded those based on cohort studies and those based on simple models (that is not a meta-analysis nor a formal decision analytic model)

Included papers were reviewed by a health economist. In the evidence tables costs are reported as given in the paper. However, where costs were in a currency other than pounds sterling, US dollars or euros, the results were converted to pounds sterling using the relevant purchasing power parity for the study year.

We have included studies from all over the world in our review, however, we use overseas studies with caution since resource use and especially unit costs vary considerably. Particular caution is applied to studies with predominantly private health insurance (For example, USA or Switzerland) where unit costs may be much higher than in the UK and to developing countries where costs may be much lower.

Each study was categorised as one of the following: cost analysis, cost-effectiveness analysis, cost–utility analysis (that is, cost–effectiveness analysis with effectiveness measured in terms of QALYs), or cost consequences analysis. We did not find any 'cost benefit analyses' (studies that put a monetary value on health gain).

Models are analogous to systematic reviews as they are pooling evidence from a number of different studies and therefore if well-conducted they should out-rank studies based on a single RCT. Statistical significance is not usually applicable to models and uncertainty is explored using sensitivity analysis instead. Hence the results reported in our economics literature review evidence tables and write-up may not necessarily imply statistical significance. In our own cost-effectiveness analysis we rigorously explore the effects of sample variation using Monte Carlo simulation (Chapter 13).

### 3.12.2 Cost-effectiveness modelling

A comprehensive cost-effectiveness analysis was developed because we found great inconsistency in the economic evaluations in the published literature. This was mainly because the evaluations varied in the clinical studies they included and because they used crude methods to deal with indirect evidence. Furthermore most of the published studies did not evaluate cost-effectiveness using NICE's reference case.

The details of the model methods are reported in chapter 13 and appendix G. The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.

- The model was based on a mixed-treatment comparison meta-analysis derived from the systematic review of clinical evidence.

- Model assumptions were reported fully and transparently.

- The results were subject to thorough sensitivity analysis and limitations discussed.

- Costs were calculated from a health services perspective.

## 3.13 Development of the recommendations

Over the course of the guideline development process the GDG was presented with the following:

- Evidence tables and narrative summaries of the clinical and economic evidence reviewed. All evidence tables are in appendix D

•Forest plots of direct meta-analyses. (appendix E)

• Forest plots of mixed-treatment meta-analyses (appendix F)

• A description of the methods and results of the cost-effectiveness analysis (appendix G)

We used the relative effectiveness evidence for all surgeries when writing recommendations for specific surgeries. This was because we found no convincing statistical evidence of any differences in relative effectiveness by type of surgery, nor was there perceived to be any clinical rationale for the assumption that type of surgery should influence the action of any of the methods of prophylaxis covered. The recommendations were explicitly linked to the relative effectiveness evidence but tempered by risk and other factors specific to the type of surgery or patient group that would affect the choice/use of specific methods of prophylaxis.

We used a modified version of the nominal group technique of consensus development to agree the final recommendations.

### 3.14 Grading of recommendations

Following a public consultation in April 2006 NICE is no longer publishing grades alongside recommendations contained within its guidance.

### 3.15 Recommendations for research

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as the importance to patients or the population, national priorities, and the potential impact on the NHS and future NICE guidance.

### 3.16 Prioritisation of recommendations for implementation

To assist users of the guideline in deciding the order in which to implement the recommendations, the guideline development group identified ten key priorities for implementation. The decision was made after discussion and voting by the GDG. They selected recommendations that would:

• Have a high impact on patient outcomes, including mortality and morbidity

• Have a high impact on reducing variation

• Lead to a more efficient use of NHS resources

• Mean patients reach critical points in the care pathways more quickly

### 3.17 *Validation of the guideline*

Registered stakeholders were given the opportunity to comment on the draft guideline, which was posted on the NICE website. A Guideline Review Panel also reviewed the guideline and checked that stakeholders' comments had been addressed.

### 3.18 Related NICE guidance

NICE is developing the following guidance (details available from www.nice.org.uk):

• Thrombophilia screening for the diagnosis of individuals at high risk of thrombosis. NICE technology appraisal guidance. (Publication date January 2008)

• Idraparinux sodium for the treatment of recurrent thromboembolism. NICE technology appraisal guidance. (Publication date TBC)

### 3.19 Updating the guideline

NICE clinical guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence 2 and 4 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendation.

# 4 Risk factors

A patients' risk of developing venous thromboembolism is determined by the type of surgery they are undergoing and by individual patient risk factors. In this chapter we examine these in turn.

## 4.1 Surgical risk

Type of surgery determines the risk of major bleeding as well as the risk of VTE. To assess which types of surgery have the highest risk we have extracted data from three different sources:

a) randomised controlled trials

b) NHS Hospital Episode Statistics (HES)

c) incidence studies.

### 4.1.1 Evidence from randomised controlled trials

For each category of surgery, the number of each event across the nil arms of RCTs included in our review (Chapters 5-7) were aggregated and divided by the aggregate sample size from the same arms. Studies were excluded if they reported any form of background prophylaxis other than early mobilisation. However, some patients may have had off-protocol prophylaxis at the discretion of their physicians.

The incidence of DVT, symptomatic pulmonary embolism (PE) and major bleeding, were estimated from the RCTs in our clinical review by a fixed effects meta-analysis, which used a Freeman-Tukey arcsine transformation to stabilise the variances of the individual study proportions[371] (Table 2 and Table 3). The types of surgery with the highest risk of DVT and symptomatic PE were (major) orthopaedic surgery followed by (major) general surgery and then neurosurgery. Gynaecological surgery had the highest risk of major bleeding.

The advantages of using this data is that patients are being systematically followed up, their VTEs are confirmed using objective tests and they are not routinely given prophylaxis (so we can estimate their risk in the absence of prophylaxis). However, the drawback is that the studies can have rather specific populations, often with patients at low risk and/or high risk deliberately excluded. This means that the data may not be generalisable. Furthermore, for some categories of surgery the sample size was small.

**Table 2:Risk of DVT and, symptomatic pulmonary embolism by type of surgery, from the no prophylaxis arm of RCTs**

| | Number of patients with an event | Sample Size | Incidence | Incidence Lower 95% CL | Incidence Upper 95% CL |
|---|---|---|---|---|---|
| **DVT** | | | | | |
| Cardiac[41,297] | 10 | 65 | 14% | 7% | 24% |
| General[4,13,51,65,83,86,93,101,144,198,203,204,236,249,313,314,324,336,350,404,405,414,423,439-441,447,475,478,479,500,520,521,531,578,583,585] | 569 | 2286 | 24% | 23% | 26% |
| Gynaecology[29,69,102,103,106,344,425,512,522,558] | 113 | 691 | 16% | 13% | 19% |
| Neurological[87,95,367,488,523,524,526,559] | 91 | 446 | 20% | 17% | 24% |
| Orthopaedic (Elective hip)[1,11,39,99,128,130,163,182,184,211,217,239,258,261,284,320,340,341,349,359,471,517,527,560,580] | 521 | 1165 | 44% | 42% | 47% |
| Orthopaedic (Hip fracture)[70,147,159,184,210,228,267,271,312,321,324,383,384,384,387,428,492,508,579,582] | 476 | 1232 | 37% | 35% | 40% |
| Orthopaedic (Elective knee)[251,326,362,369,572,574] | 99 | 322 | 27% | 22% | 32% |
| Orthopaedic (Mixed)[6,26,67,250,419,575] | 66 | 140 | 47% | 39% | 55% |
| Urological[107,225,226,325,543] | 18 | 144 | 10% | 6% | 15% |
| Vascular[494] | 2 | 19 | | | |
| Mixed[22,52,100,104,137,183,184,244,262,280,346,469,503] | 286 | 1303 | 22% | 19% | 24% |
| Not known[90,290,304,308,586] | 102 | 276 | 36% | 31% | 42% |
| **All** | **2353** | **8089** | **29%** | | |
| | | | | | |
| **Symptomatic Pulmonary embolism** | | | | | |
| Cardiac | 0 | 0 | | | |
| General[4,203,237,314,315,336,405,417,440,531] | 72 | 3044 | 1% | 1% | 2% |
| Gynaecology[102,103,106] | 2 | 250 | 1% | 0% | 3% |
| Neurological[488,526] | 0 | 129 | | | |
| Orthopaedic (Elective hip)[239,258,261,284,341,517,560,580] | 21 | 493 | 3% | 2% | 5% |
| Orthopaedic (Hip fracture)[70,147,150,159,321,383,384,387,428] | 48 | 870 | 6% | 4% | 7% |
| Orthopaedic (Elective knee)[572] | 0 | 32 | | | |
| Orthopaedic (Mixed)[26,570] | 23 | 134 | 19% | 13% | 25% |
| Urological[40,107] | 2 | 41 | 9% | 3% | 19% |
| Vascular[494] | 0 | 19 | | | |
| | | | | | |
| Mixed[244,296] | 7 | 711 | 1% | 1% | 2% |
| Not known | 0 | 0 | | | |
| | **175** | **5723** | **3%** | | |

**Table 3: : Risk of major bleeding, by type of surgery, from the nil arm of RCTs**

| | Number of patients with an event | Sample Size | Incidence | Incidence Lower 95% CL | Incidence Upper 95% CL |
|---|---|---|---|---|---|
| **Major bleeding** | | | | | |
| Cardiac[41] | 1 | 25 | | | |
| General[4,28,51,144,198,203,237,249,273,310,313,324,405,414,417,423,439,441,475,518,531,578,583,585] | 83 | 3980 | 2% | 1% | 2% |
| Gynaecology[102,344,425,512,558] | 13 | 306 | 4% | 2% | 7% |
| Neurological[95,367] | 1 | 113 | 2% | 0% | 5% |
| Orthopaedic (Elective hip)[1,11,39,128,130,211,217,320,341,349,471,527,560] | 12 | 630 | 2% | 1% | 3% |
| Orthopaedic (Hip fracture)[70,147,150,210,267,271,321,324,383,384,428,579,582] | 26 | 1001 | 2% | 1% | 3% |
| Orthopaedic (Elective knee)[326,362,369,574] | 1 | 263 | 1% | 0% | 2% |
| Orthopaedic (Mixed)[6,67,419,575] | 0 | 58 | | | |
| Urological[14,40,226,325,543] | 2 | 170 | 2% | 0% | 4% |
| Vascular[494] | 0 | 19 | | | |
| | | | | | |
| Mixed[52,100,137,280,296,454] | 2 | 1153 | 0% | 0% | 1% |
| Not known[90,290,308,309,586] | 2 | 254 | 1% | 0% | 3% |
| **All** | **143** | **7972** | **2%** | | |

### 4.1.2 Evidence from NHS Hospital Episode statistics

To find data that was less selective we turned to the NHS Hospital Episode Statistics. This database holds data on every patient admitted to an NHS hospital in England. We extracted data from the year 2003/4.

We identified all patients with a secondary diagnosis of symptomatic DVT or pulmonary embolism (ICD10=I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82.1, I82.2, I82.8, I82.9) but excluded those that had not been admitted for surgery. We grouped the patients according to their type of surgery; the surgeons on the GDG combined the surgical groups in to broader clinically meaningful categories. We then calculated the incidence of VTE for each surgical procedure using the total number of procedures performed over that period as the denominator.

Table 4 shows the different surgical categories in order of the incidence of symptomatic VTE. The types of surgery with the highest risk of VTE are cardiothoracic, major orthopaedic and vascular surgery followed by major abdominal general surgery.

While this analysis has the advantage of using data from every NHS admission, there are a number of limitations. We can't be sure that all the VTEs initially occurred after surgery; the surgery could be incidental in some cases.

However, it is more likely that events are under- rather than over-diagnosed for the following two reasons. First, a number of patients will be receiving thromboprophylaxis. We do not know what proportion of patients received prophylaxis and this is likely to vary greatly between types of surgery. It is likely that complications such as VTE could go undiagnosed or unreported. And they could be diagnosed while the patient is in the community (for example, as fatal pulmonary embolisms or non-fatal events treated on an outpatient basis). Whether or not a VTE is picked up during the hospital stay could be correlated with the length of stay and therefore the under-reporting of VTE could be greater in types of surgery with short length of stay. It is difficult to control for this, since length of immobility is also a determinant of VTE risk.

**Table 4: Incidence of symptomatic VTE by type of Surgery, as recorded in HES**

| | Number of patients with an event | Sample Size | Incidence |
|---|---|---|---|
| Femoral head | 237 | 23538 | 1.01% |
| Knee replacement | 493 | 52535 | 0.94% |
| Vascular | 1186 | 169218 | 0.70% |
| Adult cardiac | 208 | 40180 | 0.52% |
| Hip replacement | 293 | 57899 | 0.51% |
| Transplantation | 11 | 2375 | 0.46% |
| Thoracic | 117 | 26002 | 0.45% |
| Lower gastrointestinal (GI) | 428 | 95968 | 0.45% |
| Renal replacement | 140 | 39733 | 0.35% |
| Upper gastrointestinal (GI) | 356 | 110562 | 0.32% |
| Fractures | 555 | 181346 | 0.31% |
| Intensive Therapy Unit (ITU) | 1215 | 448253 | 0.27% |
| Oncology | 1311 | 529069 | 0.25% |
| Radiology cardiovascular | 404 | 221317 | 0.18% |
| Endoscopic and percutaneous | 2383 | 1376236 | 0.17% |
| Joints other | 29 | 17553 | 0.17% |
| Spine | 76 | 56559 | 0.13% |
| Orthopaedic (other) | 254 | 219116 | 0.12% |
| Neurosurgery not spine | 229 | 215533 | 0.11% |
| Plastic | 259 | 314817 | 0.08% |
| Urology | 121 | 164362 | 0.07% |
| Hernia | 72 | 115703 | 0.06% |
| Gynaecological | 179 | 443529 | 0.04% |
| Arthroscopy | 34 | 112123 | 0.03% |
| Anus and piles | 26 | 86671 | 0.03% |
| Breast | 22 | 78547 | 0.03% |
| Ear, Nose and Throat (ENT) | 51 | 209680 | 0.02% |
| Head and neck | 16 | 80258 | 0.02% |
| Max facial dental | 34 | 184784 | 0.02% |
| Eyes | 69 | 457382 | 0.02% |

### 4.1.3 Evidence from incidence studies

Both the RCT data and the HES data have major limitations for the estimation of the risk of VTE. We therefore supplemented the data with other incidence studies. The studies we found were rather heterogeneous in terms of outcomes, patients and methods (Evidence Table 1, Appendix D).

One study[564] evaluated the incidence of symptomatic VTEs using a database of 1.7 million patients in 76 surgical categories in the USA. They included cases of symptomatic VTE occurring during either the initial hospitalisation or a subsequent hospitalisation within 91 days of the surgery. They distinguished between patients with and without malignancy. Non-malignant categories with an incidence greater than 2% were:

- Embolectomy or endarterectomy of lower limb artery 2.8%
- Total hip arthroplasty 2.4%
- Neurosurgery involving excision/destruction or biopsy of brain tissue 2.3%
- Partial hip arthroplasty 2.0%

Among the patients with cancer a number of additional categories were over 2%:

- Permanent colostomy 2.6%
- Radical cystectomy 3.7%
- Percutaneous nephrostomy 3.6%
- Exploratory laparotomy 2.4%
- Internal fixation of femur 3.0%

In patients without a malignancy, gynaecological and head and neck, and laparoscopic abdominal surgery conveyed the lowest risk of VTE.

The other studies[19,24,63,161,161,198,248,266,287,354,358,381,418,418, 452,452,486,530,530,555] we found are difficult to summarise, because of their heterogeneity, but if we compare the incidences with those in Table 2, it would seem that there is a relatively high risk of VTE associated with prostatectomy, gynae-oncological surgery and neurosurgery and a low risk associated with surgery for breast cancer or head and neck/ENT surgery.

The data reported in this section is limited because of the heterogeneity of the methods used by the different studies and because it is difficult to control for the use of prophylaxis or anaesthesia.

### 4.1.4 Discussion of data on surgical risk

We used different sources to estimate the risk of VTE for different categories of surgery. As predicted the incidence figures for VTE estimated using HES data were much lower than other estimates, implying under-reporting and/or treatment in the community. This was true even when compared to a similar database in the USA[564].

Hip surgery (elective and hip fracture) had higher rates of VTE by all three approaches. Some categories of cardiothoracic, vascular, urological, neurological and general surgery were also high risk, although, the rankings were not necessarily the same for the different approaches. Except for cancer-related surgery, gynaecological surgery had low rates of VTE by all three approaches – this could in part be due to these patients being younger on average than some of the other patient groups.

Comparisons between different categories of surgery are likely to be confounded by age and differences in prophylaxis and anaesthesia usage. Length of stay is likely to be a contributory factor since immobility is a causal mechanism. However it might also be a confounder since the longer people stay in hospital the more likely that their VTE will be recorded.

The differences in incidence within the broad surgical categories are probably much greater than the differences between categories[564].

The strategy that the GDG adopted from this evidence was to consider major orthopaedic surgery as higher risk for VTE than cardiac, thoracic, urological, vascular, gynaecological, neurological and general surgery. Within orthopaedic surgery, hip fracture was considered to be highest risk followed by elective orthopaedic procedures and then other types of major orthopaedic surgery.

The GDG decided that the no-prophylaxis arms of the RCTs was the best source for the baseline risk of VTE and major bleeding, and this was used in our cost-effectiveness analysis (Chapter 13). The advantage of these risk estimates is that they control for prophylaxis use. However, the GDG acknowledged also the weaknesses in this data. Firstly trial populations might not be representative of surgical patients in general. Second, it has been postulated that the incidence of VTE has fallen over time due to prophylaxis use but also due to other factors. If this is true then the RCT evidence, which goes back to the 1970s may over-estimate the risk of DVT and PE. Conversely, since RCT protocols usually involve surveillance for asymptomatic DVT, they might under-estimate the incidence of PE if DVTs are being diagnosed and actively before the time when they would have become symptomatic in a non-trial setting.

## 4.2 Patient risk factors

Patient susceptibility to DVT and PE varies according to their individual risk factors as well as the surgical risk. Some risk factors are more important than others. The aim of this review is to determine risk estimates for specific factors.

We searched for systematic reviews on patient factors and whether they increase the risk of developing a DVT or PE. Initially, we confined the search to surgical patients. We identified one study that included several systematic reviews encompassing various risk factors in surgical patients[142]. The search was extended to any patient group exposed to a risk factor when insufficient information was found in surgical populations. Several reviews were identified for non-surgical populations[23,133,180,289,370,449,463]. Some reviews only included studies that used an objective test for diagnosing venous thromboembolism such as a fibrinogen uptake or ultrasound, whereas others did not report the method of diagnosis for studies included. The number of cases and controls was not always reported. Details for each systematic review are reported below. We also referred to previous guidelines for their included risk factors[189,476].

### 4.2.1 Age

Edmonds et al[142] identified six studies investigating the association between age and postoperative DVT (evidence level 2+). There was a general trend of increased age being associated with an increased risk of DVT in all studies. Two of the studies showed the incidence of DVT to be higher in those over 60 than those under; two studies showed the mean age of patients with DVT to be higher than those without DVT; and two studies showed an incremental increase associated with increasing age, one of them finding the risk to be constant at below 45 years of age. A pooled risk estimate was not possible because of the different ways of investigating across the studies. (Evidence Table 2, Appendix D).

### 4.2.2 Obesity

Edmonds et al[142] identified seven studies investigating the association between obesity and postoperative DVT (evidence level 2+). Five out of the seven studies found a significant association between an increase in obesity and risk of DVT and two found no significant difference. A pooled estimate was not possible because of different definitions for obesity used across the studies. (Evidence Table 3, Appendix D). We used the definition of obesity as being patients with a body mass index greater than or equal to 30kg/m$^2$ which is the definition used in the current NICE guidelines[388].

### 4.2.3 Past history of venous thromboembolism

Edmonds et al[142] identified four studies investigating the association between a history of venous thrombosis and postoperative DVT (evidence level 2+). When three of the studies were pooled, they indicated a significant association between past history of venous thrombosis and risk of DVT (OR=5.18, 95% CI: 3.16 to 8.49). The other study suggested no difference but did not provide any data. (Evidence Table 4, Appendix D).

### 4.2.4 Thrombophilia

Thrombophilias are the genetic or acquired prothrombotic states that increase the tendency to venous thromboembolism (Evidence Table 5, Appendix D).

Edmonds et al[142] identified two studies investigating the association between activated protein C (APC) resistance or Factor V Leiden (FVL) mutation and postoperative DVT (evidence level 2+). One study reported low sensitivity to APC was shown to be significantly associated with postoperative DVT (RR=4.9, 95% CI: 1.1 to 22.2) with 95% of the cases being attributable to the FVL mutation. The second study reported that a low sensitivity of FVL to APC (OR=2.97, 95% CI: 1.27 to 6.92) and FVL mutation (OR=3.18, 95% CI: 0.99 to 10.2) were associated with postoperative DVT.

Two of the studies included in the review by Edmonds et al[142] examined antithrombin deficiency (evidence level 2+). One found patients who developed postoperative DVT had a lower level of antithrombin, the other did not find any association. We also identified one systematic review that looked at deficiency in antithrombin, protein C or protein S[463]. All three were associated with an increased risk of postoperative venous thromboembolism with relative risks of 5, 6.5 and 1.7 respectively. No information was given as to how venous thrombosis was diagnosed. Edmonds et al[142] found no surgical studies investigating other thrombophilias.

We identified one systematic review with 25 studies that looked at the association for lupus anticoagulants and/or anticardiolipin with thrombosis (venous or arterial) in medical populations[180] (evidence level 2+). Results were grouped according to type of event: first event, recurrent event or any event (distinction between first and recurrent events not possible). Lupus anticoagulants were found to be significantly associated with DVT. Five studies investigating lupus anticoagulants and anticardioplatin antibodies gave pooled odds ratios of 5.71 for any event and 9.4 for a first event. None of the studies showed a significant association with anticardioplatin antibodies. Four studies investigating lupus anticoagulants alone gave pooled odds ratios of 16.2 for any event and 4.01 for a recurrent event.

We identified one systematic review with 24 studies that looked at the association between raised homocysteine levels and venous thrombosis[133] (evidence level 2+). No information was given as to how venous thrombosis was diagnosed. The review showed that a 5µmol/L increase in measured plasma total homocysteine is associated with an increased risk of venous thrombosis (OR=1.27, 95% CI: 1.01 to 1.59 from three prospective studies, OR=1.60, 95% CI: 1.10 to 2.34 from 24 retrospective studies). The same review also looked at the association of MTHFR (Methylenetetrahydrofolate reductase) with venous thrombosis. The 677TT genotype was associated with a 20% higher risk of venous thrombosis compared to the 677CC genotype (OR=1.20, 95% CI: 1.08 to 1.32).

We identified one systematic review that looked at the association between prothrombin gene mutation and venous thromboembolism[463] (evidence level 2+). In one study G20210a prothrombin was associated with a three fold increase in risk of venous thromboembolism (OR=2.8, 95% CI: 1.4 to 5.6). Similar results were found in a pooled analysis of eight case-control studies (OR=3.8, 95% CI: 3.0 to 4.9).

Samama et al also looked at the association between elevated plasma levels of coagulation factors and venous thromboembolism[463]. Elevated factor VII, VIII, IX and XI were all found to be significantly associated with venous thromboembolism while elevated factor X or high plasma levels of fibrinogen were not.

### 4.2.5 Varicose veins

Edmonds et al[142] identified seven studies investigating the association between varicose veins and postoperative DVT (evidence level 2+). A pooled estimate of the six studies with data showed an increase risk (OR 2.39, 95% CI: 1.69 to 3.37). One study did not provide any data (Evidence Table 6, Appendix D).

### 4.2.6 Cardiovascular factors

Edmonds et al[142] identified two studies looking at the association between cardiovascular factors and postoperative DVT (evidence level 2+). Three potential risk factors were identified: recent myocardial infarction, hypertension and congestive cardiac failure. None were shown to be significantly associated with postoperative DVT. Congestive cardiac failure was shown to be significantly associated with DVT in univariate analysis but not in multivariate analysis in two studies, suggesting that the association was potentially explicable by confounding. Another non-surgical study reported by Edmonds showed similar results (Evidence Table 7, Appendix D).

### 4.2.7 Oral contraceptives

Edmonds et al[142] identified five cohort studies and two case control studies in surgical patients (evidence level 2+). A pooled risk estimate was only possible for three of the studies due to deficiencies in reported data. This showed oral contraceptive pills were significantly associated with an increased risk of postoperative DVT (OR=2.48, 95% CI: 1.53 to 4.02). Edmonds et al. reported some weaknesses with the data available: the studies were somewhat dated and may not apply to the recent third generation of oral contraceptive pills; and only three out of the five cohort studies screened everyone for DVT. Another systematic review compared third generation with second generation users in non-surgical populations[289] (evidence level 2+). Third generation contraceptives were associated with an increased risk of venous thrombosis compared to second generation contraceptives (unadjusted OR=1.6, 95% CI: 1.3 to 1.9; adjusted odds ratio OR=1.7, 95% CI: 1.4 to 2.0) (Evidence Table 8, Appendix D).

The Royal College of Obstetricians and Gynaecologists offers guidance on venous thromboembolism and hormonal contraceptives[450]. They recommend: combined oral contraception should be discontinued 4 weeks before major surgery when immobilisation is expected; progestogen only methods need not be discontinued prior to surgery even when immobilisation is expected; and hormonal methods do not need to be discontinued before minor surgery without mobilisation.

### 4.2.8 Hormone replacement therapy

Edmonds et al[142] found no studies investigating hormone replacement therapy in a surgical population. We identified two recent systematic reviews that identified studies from a non-surgical population. The Royal College of Obstetricians and Gynaecologists[449] identified nine studies but did not pool the relative risks, these varied from 2.1 to 6.9 (evidence level 2+). Miller et al[370] calculated a pooled relative risk of 2.14 (credible interval 1.64 to 2.81) from 12 studies (evidence level 2+). Six of these studies also compared the risk of oral contraceptive use in the first year compared to subsequent years of use. Use in the first year had a higher risk estimate (relative risk in first year of use: 3.49, credible intervals: 2.33 to 5.59; relative risk in subsequent years of use: 1.91, credible intervals: 1.18 to 3.52) (Evidence Table 9, Appendix D).

The Royal College of Obstetricians and Gynaecologists offers guidance on hormonal replacement therapy and venous thromboembolism[449]. They recommend that HRT should be considered a risk factor for VTE but it is not necessary to stop prior to surgery provided that appropriate thrombo- prophylaxis is used.

### 4.2.9 Cancer

Edmonds et al[142] identified nine studies investigating the association between cancer and postoperative DVT (evidence level 2+). An assumption in the review is that an effect of cancer on thrombosis following general surgery is the same as the effect when surgery is for the treatment of that cancer. All nine studies found an increased risk associated with cancer giving a pooled odds ratio of 2.94 (95% CI: 2.01 to 4.29). Around a third of the total number of patients also received thromboprophylaxis (Evidence Table 10, Appendix D).

### 4.2.10 Chemotherapy

No surgical studies were found investigating the association between chemotherapy and postoperative DVT. We identified one systematic review of 32 studies that investigated vascular and neoplastic events associated with tamoxifen in non-surgical patient groups (evidence level 1+). Eleven of the included studies reported pulmonary embolisms and demonstrated overall a significantly increased risk of pulmonary embolism (RR=1.88,

95% CI: 1.17 to 3.01) and 15 of the included studies reported DVT also demonstrating an increased risk(RR=1.87, 95% CI: 1.33 to 2.64). Seven of the 11 pulmonary embolism studies and 11 of the 15 DVT studies investigated the use of tamoxifen in patients with malignancy. The other four studies were for the prevention of cancer (Evidence Table 11, Appendix D).

### 4.2.11 Smoking

Edmonds et al[142] identified four studies investigating the association between smoking and postoperative DVT (evidence level 2+). Two studies showed smokers to have significantly less DVTs than non-smokers; one study showed smoking to be protective in a univariate analysis but not in a multivariate analysis and the fourth study showed no difference. Overall, the studies suggest a non-significant association of fewer postoperative DVTs for smokers despite studies indicating it to be a risk factor for DVT in the general population. However, smoking is associated with other postoperative adverse events such as wound related or cardiopulmonary complications.

### 4.2.12 Prolonged travel

Immobility associated with prolonged and continuous travel immediately before or after surgery may increase a patient's risk of developing postoperative VTE. We found no studies that specifically addressed this patient group. We identified one systematic review that investigated venous thromboembolism risk in long distance travel[23] (evidence level 2+). Long haul travel was shown to significantly increase risk (OR=1.59, 95% CI: 1.04 to 2.43) in three case control studies, RR=2.93, 95% CI: 1.58 to 5.58 from two cohort studies). Two of the studies provided a risk estimate for any form of long distance travel, these also showed an increase risk of venous thrombosis (OR=2.6, 95% CI: 1.79 to 3.79). All the studies related to travel were in journeys over three hours. In three, travel related to the previous four weeks and in the fourth, travel related to the previous three weeks. Meaningful comparison between patients travelling for surgery and data from people on long haul flight is difficult. Long haul flight travellers are often healthier than the general population and, therefore, not a true sample[23] (Evidence Table 12, Appendix D)

### 4.2.13 Other risk factors for venous thromboembolism

Two guidelines, not specifically in surgical patients, considered risk factors for venous thromboembolism[189,476]. In addition to the risk factors listed above the following were identified: acute medical illness, recent myocardial infarction/stroke; heart/respiratory failure, inflammatory bowel disease(e.g.ulcerative colitis/Crohn's disease), nephrotic syndrome; myeloprofilerative disease; paraproteinaemia; pregnancy or puerperium, severe infection, paroxysmal nocturnal haemoglobinuria and Behcet's Disease.

### 4.2.14 Discussion of data on patient risk

The identified systematic reviews of patient related risk factors varied in the quality of their evidence: the diagnosis of venous thromboembolism was not always achieved using an objective test (for example fibrinogen uptake test, ultrasound); only some of the studies provided the number of cases and controls on which the data was based; some studies gave pooled risk ratios for their results while others only provided the risk ratios for individual studies. Evidence was not always available from a surgical population. In these cases evidence from other systematic reviews and guidelines was used to help identify risk factors.

The evidence suggests a history of venous thromboembolism, thrombophilias, cancer, varicose veins, oral contraceptives, obesity and increasing age are all significant risk factors for postoperative venous thromboembolism. Evidence from other systematic reviews and guidelines show that hormone replacement therapy, chemotherapy agents, immobility (including a leg in plaster cast or paralysis), prolonged travel, acute medical illness, recent myocardial infarction or stroke, heart or respiratory failure, inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease), nephrotic syndrome, myleoprofilerative disease, paraproteinaemia, pregnancy or puerperium, severe infection, paroxysmal nocturnal haemoglobinuria, Bechet's dsease and inherited thrombophilias are also risk factors for venous thromboembolism.

Increasing age was also associated with an increase with postoperative DVT. The studies using a cut-off to examine a difference between age selected 60 years and those below 45 years were found to at the same lower risk of developing postoperative DVT. Other guidelines have put an age threshold of 40. We were unable to find an evidence based justification for an age cut off of 40 for the higher risk patients covered by our guideline. White et al[563] found that the relationship between age, type of surgery and risk is complex. In particular there is no evident step up in risk at 40. Anderson & Spencer[17] noted stratification of risk by the simple dichotomy of age below or above 40 years fails to account for the significantly higher risk among the elderly patients undergoing high risk surgical procedures.

The evidence for risk factors is hetrogenous in several ways:

- only some of our evidence comes from surgical populations and is directly applicable to our patient group

- the way risk is measured differed between studies, some use odds ratios while others use relative risk

- the amount and quality of the evidence differed considerably between risk factors.

Our scope is "major surgery" and by this we mean all operations where patients are admitted for their operation. This includes the large number of routine planned operations. Within this group there will be those who are at a different levels of risk of developing VTE. Because of the uncertainty of how to use the risk factor evidence, and the different levels of risk within our included patients we have opted for a simplified approach to the recommendations. Within each surgery type, those without any risk factor receives one level of prophylaxis, and those with one or more risk factors receive another level of prophylaxis (Chapter 14: Surgical Specialities).

There was evidence that prolonged travel of more than 3 hours increased the risk of VTE. Studies varied in the time period over which the risk was considered to remain elevated, but it was either 3 or 4 weeks in all. As well as being including this on the list of individual patient related risk factors, the GDG recommend that patients are informed of the risks of continuous travel of more than 3 hours in the 4 weeks before or after surgery so that they can make informed choices and avoid increasing their risk where possible.

The GDG used both the evidence from systematic reviews and The Royal College of Obstetricians and Gynaecologists guidance on venous thromboembolism and hormonal contraceptives[450] in recommending that consideration be given to stopping combined oral contraceptives four weeks before elective surgery.

## 4.3 Recommendations

**Box 1: Individual patient-related risk factors for venous thromboembolism**

- Active cancer or cancer treatment
- Active heart or respiratory failure
- Acute medical illness
- Age over 60 years
- Antiphospholipid syndrome
- Behcet's disease
- Central venous catheter in situ
- Continuous travel of more than 3 hours approximately 4 weeks before or after surgery
- Immobility (for example, paralysis or limb in plaster)
- Irritable bowel disease (for example, Crohn's disease or ulcerative colitis)
- Myeloproliferative diseases
- Nephrotic syndrome
- Obesity (body mass index $\geq$ 30 kg/m$^2$)
- Paraproteinaemia
- Paroxysmal nocturnal haemoglobinuria
- Personal or family history of VTE
- Pregnancy or puerperium
- Recent myocardial infarction or stroke
- Severe infection
- Use of oral contraceptives or hormonal replacement therapy
- Varicose veins with associated phlebitis
- Inherited Thrombophilias for example:
  - High levels of coagulation factors (for example, Factor VIII)
  - Hyperhomocysteinaemia
  - Low activated protein C resistance (for example, Factor V Leiden)
  - Protein C, S and antithrombin deficiencies
  - Prothrombin 2021A gene mutation

**Patients should be assessed to identify their risk factors for developing venous thromboembolism (VTE, see Box 1)**

**Healthcare professionals should inform patients that the immobility associated with continuous travel of more than 3 hours in the 4 weeks before or after surgery may increase the risk of VTE.**

**Healthcare professionals should advise patients to consider stopping combined oral contraceptive use 4 weeks before elective surgery [see Royal College of Obstetricians and Gynaecologists guideline no. 40][450].**

## 4.4 Recommendation for research

### 4.4.1 Research Question

What is the relevance of surgical procedure and patient risk factors to incidence of clinical DVT, confirmed PE, major bleeding, and other postoperative adverse outcomes (e.g. myocardial infarction, stroke) in modern surgical practice?

The aim should be to recruit patients undergoing a range of surgical procedures with different levels of expected risk of VTE, ensuring coverage of the common operations currently performed in the NHS.

Baseline evaluation would aim to identify risk factors for VTE and for other adverse outcomes (e.g. bleeding and occlusive vascular events). The study would also record any in-hospital drug treatment and discharge medication. Note, however, that this would be a large observational cohort study and would not be appropriate for determining the effects of treatment, since moderate effects cannot be assessed reliably by such studies.

The control (reference) group will be defined, for each parameter (e.g. age) by a category of patients at low risk of VTE (e.g. age < 30).

### 4.4.2 Why this research is important

The chief difficulty faced when formulating the present guideline was the absence of accurate estimates of VTE risk in the modern era. Although it was possible to estimate the relative risk reductions associated with particular interventions, it was not possible to estimate their associated absolute benefits. It is possible that the modern risks of VTE are much lower than is represented by the available trial evidence. Information on absolute risks of VTE (and other postoperative complications) needs to be obtained in order to assess cost effectiveness reliably.

Information from this study would help surgical teams to provide their patients with accurate information about the balance of benefit and risk associated with particular interventions.

This study could be performed easily if the design elements were kept simple, with one-sided forms that could be completed at discharge, and follow-up through mailed questionnaires and tracking of mortality via the Office of National Statistics.

# 5 Mechanical Methods of Prophylaxis

## 5.1 Introduction

Venous stasis in the deep leg veins causes a decrease in the mean flow and pulsatility of the venous flow trace. Mechanical methods of DVT prophylaxis work to combat venous stasis and include:

- compression devices such as
  - graduated compression stockings (GCS)
  - intermittent pneumatic compression (IPC)
  - foot impulse device (FID) (also known as foot pumps
- electrical stimulation (ES).

Unlike pharmacological prophylaxis, mechanical methods are not associated with bleeding risks.

### Graduated Compression Stockings (GCS)

Graduated compression stockings exert graded circumferential pressure from distal to proximal regions of the leg, increasing blood velocity and promoting venous return. There are two different standards for graduated compression stockings, the British Standard and the European Standard (table 5). A graduated compression pressure profile of 18mmHg at the ankle, 14mmHg at the mid calf, 8mmHg at the popliteal region, 10mmHg at the lower thigh and 8mmHg at the upper thigh increases deep venous flow velocity by 75%[484]. This relates to British Standard Class II and European Standard Class I.

GCSs should not be used if the patient has peripheral arterial disease, arteriosclerosis, severe peripheral neuropathy, massive leg oedema or pulmonary oedema, oedema secondary to congestive cardiac failure, local skin/soft tissue diseases such as recent skin graft or dermatitis, extreme deformity of the leg, gangrenous limb, doppler pressure index < 0.8, or gross limb cellulitis.

**Table 5: Comparison of British and European standard compression stockings' profiles**

| Class of stockings | British Standard | European Standard |
|---|---|---|
| I | 14-17 mmHg | 18.4-21.1 mmHg |
| II | 18-24 mmHg | 25.2-32.3 mmHg |
| III | 25-35 mmHg | 36.5-46.6 mmHg |

### Intermittent Pneumatic Compression (IPC) Devices

IPC devices involve the use of inflatable garments wrapped around the legs, which are inflated by a pneumatic pump. The pump provides intermittent cycles of compressed air which alternately inflate and deflate the chamber garments, enhancing venous return[199]. It combats VTE through its haemodynamic effect on preventing venous stasis and by stimulating fibrinolytic activity[502]. This fibrinolytic mechanism is involved in the dissolution of clot and prevention of thrombus formation[353].

### Foot Impulse Devices (FID)

Foot impulse devices (or foot pumps) increase venous outflow and reduce stasis in immobilised patients. The haemodynamic effect of the pumping mechanism in the sole of the foot is activated by weight bearing[187]. On weight bearing the venous plexus in the sole is rapidly emptied into the deep veins of the legs. The pulsatile flow produced by walking prevents thrombus formation. It is within this physiological mechanism that the foot impulse device is designed to stimulate the venous pump artificially by compressing the venous plexus and mimicking normal walking and reducing stasis in immobilised patients.

### Electrical Stimulation

Electrical stimulation (ES) devices are designed to increase venous blood flow velocity out of the leg to reduce the incidence of post-surgical venous thrombosis. Electrical stimulation-induced

contractions have been shown to activate the skeletal muscle pump, promote limb blood flow, and may be effective for reducing venous pooling/stasis and oedema[154].

## 5.2 Clinical evidence on mechanical compression methods alone

We examined the evidence for the effectiveness of using mechanical prophylaxis compared to using no prophylaxis.

### 5.2.1 Graduated compression stockings vs no prophylaxis

We identified nine RCTs with 1344 participants from two systematic reviews[15,444] (Evidence Table 13, Appendix D).

**Effect on DVT:** Stockings reduced the risk of DVT by 51% (RR=0.49, 95% CI: 0.35 to 0.69, 9 studies) (Figure 1, Appendix E). There was significant heterogeneity in the risk reductions observed in these studies ($\chi^2$ on 8 df =16.99, p=0.03) which appeared to be due to the inclusion of one study[250]. A subgroup analysis of the different length of stockings (Figure 2, Appendix E) showed significant heterogeneity between the groups ($\chi^2$ on 1 df =13.05, p=0.0003).. We grouped the studies into thigh length (five studies), knee length (one study), thigh and knee length (1 study) and length not specified. The study on mixed length stockings[250] seemed to contribute to this. The study in knee length stockings also showed inconclusive results[448].

**Effect on pulmonary embolism:** Two trials reported PE data. There was only one event in the two trials (RR=0.32, 95% CI: 0.01-7.67) (Figure 3, Appendix E).

**Effect on proximal DVT:** There was no significant difference between the groups (RR=0.40, 95% CI: 0.08 to 2.03, three studies) (Figure 4, Appendix E).

### 5.2.2 Intermittent pneumatic compression devices vs no prophylaxis

We identified one systematic review[444] which included 18 RCTs with 1990 participants (Evidence table 14, Appendix D). We excluded one study from our meta-analysis because it was not conducted in surgical patients.

**Effect on DVT:** IPC devices reduced the risk of DVT by 56% (RR=0.44, 95% CI: 0.33 to 0.59; 17 studies) (Figure 5, Appendix E). There was significant heterogeneity within the results ($\chi^2$ on 15 df =24.64, p=0.05) which was largely attributable to the inclusion of one study of patients undergoing pelvic surgery for malignancy[103]. In this study there were more DVTs in the group receiving IPC than the control group (the difference was not significant). The IPC devices were worn in the perioperative period only which may account for the lack of effect in this high risk group.

**Effect on pulmonary embolism:** There was no significant difference between the groups for pulmonary embolism (RR=0.82, 95% CI: 0.42 to 1.60, seven studies) (Figure 7, Appendix E).

**Effect on proximal DVT:** IPC devices reduced the risk of proximal DVT by 44% (RR=0.56, 95% CI: 0.41 to 0.78, eight studies) (Figure 8, Appendix E).

### 5.2.3 Foot impulse devices vs no prophylaxis

We identified one systematic review including two RCTs with 126 participants for this comparison[444] (Evidence table 15, Appendix D).

**Effect on DVT:** Foot impulse devices reduced the risk of DVT by 65% (RR 0.35, 95% CI: 0.19 to 0.62, two studies) (Figure 9, Appendix E).

**Effect on pulmonary embolism:** One study reported pulmonary embolism data. There were no events in either group and so the effect on PE could not be estimated (Figure 10, Appendix E).

**Effect on proximal DVT:** There was no significant difference between the groups (RR=0.09, 95% CI: 0.01 to 1.49, one study) (Figure 11, Appendix E).

## 5.3 Clinical evidence on mechanical compression methods as an adjuvant

We examined the evidence for the effectiveness of mechanical prophylaxis when used in combination with another method of prophylaxis (that is, as an adjuvant). In these studies both groups receive a background method of prophylaxis and the intervention group are given a mechanical compression device in addition to this. The background prophylaxis may be another mechanical method or a pharmacological prophylaxis.

### 5.3.1 Graduated compression stockings as an adjuvant

We identified 11 RCTs with 1371 participants from two systematic reviews[15,444] (Evidence table 16, Appendix D) that looked at the effectiveness of

GCS as an adjuvant intervention. The background prophylaxis was pharmacological in nine studies, and mechanical (IPC devices) in two.

**Effect on DVT:** Two studies added GCS to a mechanical device. There was no significant difference between groups (RR=0.49, 95% CI: 0.06-4.02) (Figure 15, Appendix E). Adding GCS to a pharmacological prophylaxis produced a 56% reduction in risk (RR=0.39, 95% CI: 0.23 to 0.66, 9 studies) (Figure 15, Appendix E). There was significant heterogeneity within the results ($\chi^2$ on 8 df =19.89; P=0.03) which may be due to the different pharmacological background methods used in the studies.

**Effect on pulmonary embolism:** No studies of GCS as an adjuvant to a mechanical device reported PE events. Where a pharmacological background was used, there was no significant difference between the groups (RR=0.34, 95% CI: 0.10 to 1.12, four studies) (Figure 17, Appendix E).

**Effect on proximal DVT:** One study that added GCS to a mechanical device reported proximal DVT with no events in either group. Adding GCS to a pharmacological prophylaxis reduced the risk of proximal DVT by 55%. (RR=0.35, 95% CI: 0.13 to 0.90, 3 studies) (Figure 18, Appendix E).

### 5.3.2 Intermittent pneumatic compression devices as an adjuvant

The HTA report[444] included seven RCTs of IPC devices as an adjuvant to another method of prophylaxis in surgical patients (we excluded one study conducted in medical patients). We identified five additional RCTs[136,149,194,298,434] published after the HTA report, making a total of 12 studies with 4244 participants (Evidence table 17, Appendix D). Four studies added IPC devices to a mechanical method, six a pharmacological prophylaxis, and in two studies IPC devices were added to a combined background therapy of stockings plus a pharmacological method.

**Effect on DVT:** No significant difference was found for DVT for any of the IPC adjuvant analyses (mechanical background: RR=0.53, 95% CI: 0.25 to 1.16, 4 studies; pharmacological background: RR=0.78, 95% CI: 0.51 to 1.20, 4 studies; mechanical and pharmacological background: RR=0.95, 95%CI: 0.63 to 1.44, 2 studies) (Figure 19, Appendix E).

**Effect on pulmonary embolism:** Adding IPC devices to a pharmacological method produced a 59% reduction in risk (RR=0.41, 95% CI: 0.25 to 0.65, five studies). This result was mainly determined by one large trial[434], which was designed and powered to analyse pulmonary embolism as its primary outcome. Adding IPC devices to another mechanical method (RR=0.51, 95% CI: 0.05 to 5.43, two studies) or to another mechanical and a pharmacological method found no significant effect (RR=1.01, 95%CI: 0.06 to 16.05, two studies) (Figure 20, Appendix E).

**Effect on proximal DVT:** No significant difference was found for proximal DVT for any of the IPC adjuvant analyses (mechanical background: RR=0.37, 95% CI: 0.08 to 1.76, three studies; pharmacological background: RR=1.01, 95% CI: 0.33 to 3.09, four studies; mechanical and pharmacological background: RR=0.84, 95%CI: 0.26 to 2.71, one study) (Figure 21, Appendix E).

### 5.3.3 Foot impulse devices as an adjuvant

Three RCTs with 208 participants looked at the effectiveness of foot impulse devices as an adjunct to another method of prophylaxis (Evidence table 18, Appendix D). The background prophylaxis was stockings in two studies[164,504] and unfractionated heparin plus aspirin in one study[498].

**Effect on DVT:** Foot pumps and stockings reduced the risk of DVT by 74% compared to stockings alone (RR=0.26, 95% CI: 0.09 to 0.70, one study)[164]. There was no significant difference when foot pumps were added to unfractionated heparin and aspirin (RR=0.09, 95% CI: 0.01 to 1.56, one study)[498] (Figure 22, Appendix E).

**Effect on proximal DVT:** Foot pumps plus stockings reduced the risk of proximal DVT by 89% compared to stockings alone (RR=0.11, 95% CI: 0.03 to 0.40, two studies) (Figure 23, Appendix E). In the study using pharmacological background prophylaxis there were no events in either group, the relative risk was therefore not estimable.

## 5.4 Comparison of mechanical compression methods

### 5.4.1 Thigh length stockings vs knee length stockings

The HTA report[444] identified two RCTs comparing thigh and knee length stockings in a total of 496 patients (Evidence table 19, Appendix D). DVT was the only outcome reported.

**Effect on DVT:** A meta-analysis of the two studies was inconclusive owing to the limited number of reported events (RR=1.01, 95% CI: 0.43 to 2.39; figure 27, Appendix E).

### 5.4.2 Thigh length stockings vs knee length stockings as an adjuvant

We identified one RCT comparing thigh with knee length stockings in 294 patients where patients in both arms also received LMWH[247] (Evidence table 19, Appendix D). There were three comparisons in the study, two types of thigh length stockings and one type of knee length. For our analysis we have combined the results for the different types of thigh length stockings together. DVT was the only outcome reported.

**Effect on DVT:** Thigh length stockings reduced the risk of DVT by 63% compared to knee-length stockings (RR=0.37, 95% CI: 0.15 to 0.89; figure 27, Appendix E).

### 5.4.3 Thigh length IPC vs knee length IPC

We identified one RCT comparing thigh with calf length IPC devices in 90 patients (Evidence table 20, Appendix D). DVT was the only outcome reported.

**Effect on DVT:** There was no significant difference between the groups (RR=0.31, 95% CI: 0.01 to 7.31; figure 28, Appendix E).

### 5.4.4 Intermittent pneumatic compression devices vs graduated compression stockings

We identified three studies with 280 participants that compared IPC devices with GCS[214,451,485] (Evidence table 21, Appendix D). In two studies patients in both arms also received a pharmacological prophylaxis, LMWH in one study[485], and aspirin in the other[451].

**Effect on DVT:** There was no significant difference between groups receiving IPC devices or stockings (RR=0.57, 95% CI: 0.12 to 2.71, one study)[214]. When LMWH was used as a background therapy, there was a reduced risk of DVT of 98% in the IPC device group (RR=0.02, 95% CI: 0.00 to 0.31, one study)[485] (Figure 29, Appendix E).

**Effect on pulmonary embolism:** One study found no significant difference between groups (RR=1.00, 95% CI: 0.07 to 15.12, one study). In the second study aspirin was used as a background prophylaxis and there were no events in either arm. (Figure 30, Appendix E).

**Effect on proximal DVT:** IPC devices reduced the risk of proximal DVT by 67% compared to GCS (RR=0.33, 95% CI: 0.12 to 0.92, two studies) when used with a pharmacological agent as background prophylaxis (Figure 31, Appendix E).

### 5.4.5 Foot impulse device vs intermittent pneumatic compression devices

We identified two studies with a total of 277 participants that compared foot impulse devices with intermittent pneumatic compression devices[20,576] (Evidence table 21, Appendix D). In one study[576], patients in both arms also wore GCS. Neither study reported proximal DVT rates.

**Effect on DVT:** There was no significant difference between the groups (RR=3.75, 95% CI 0.44 to 31.84, two studies) (Figure 32, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference between the groups (RR=2.25, 95% CI 0.24 to 21.35, two studies) (Figure 33, Appendix E).

### 5.4.6 Foot impulse devices vs graduated compression stockings

We did not identify any studies comparing foot impulse devices and graduated compression stockings that met our inclusion criteria.

## 5.5 Grouping of mechanical compression studies

For our analysis, we examined the effect of any mechanical compression method and explored whether there were differences in the magnitude of effects of different methods. The subgroups were tested for heterogeneity.

### 5.5.1 Mechanical compression vs no prophylaxis

We combined 28 studies with a total of 3334 participants comparing GCS, IPC devices or foot impulse devices with no prophylaxis.

**Effect on DVT:** Overall, mechanical compression devices reduced the risk of DVT by 54% (RR=0.46, 95% CI: 0.37 to 0.56, 28 studies) (Figure 12, Appendix E). There significant heterogeneity in the overall risk reduction. This was due to the two stocking studies and the one IPC study mentioned in the sections above. There was no significant heterogeneity in the magnitude of effect between the groups ($\chi^2$ on 2 df =2.45, p=0.29).

**Effect on pulmonary embolism**: There was no significant reduction in pulmonary embolism for all mechanical compression devices (RR=0.78, 95% CI: 0.40 to 1.50, 10 studies) (Figure 13, Appendix E). There was no significant heterogeneity between the groups ($\chi^2$ on 1 df =0.31, p=0.58).

**Effect on proximal DVT:** Overall, mechanical compression devices reduced the risk of proximal DVT by 48% compared to no prophylaxis (RR=0.52, CI 0.38 to 0.72, 12 studies) (Figure 14, Appendix E). There was no significant heterogeneity between the groups ($\chi^2$ on 1 df =2.06, p=0.15).

### 5.5.2 Mechanical compression as an adjuvant

We combined 25 studies with a total of 5432 participants comparing mechanical prophylaxis as an adjuvant to another thromboprophylaxis in order to determine the overall effect of all mechanical compression methods, and to look for differences in magnitude of effect between mechanical or pharmacological prophylaxis as background therapy.

**Effect on DVT:** Overall, mechanical compression prophylaxis as an adjuvant reduced the risk of DVT by 46% (RR=0.54, 95% CI: 0.39 to 0.73, 22 studies). Mechanical compression prophylaxis as an adjuvant to another mechanical reduced the risk of DVT by 58% (RR=0.42, 95% CI: 0.18 to 0.98, seven studies). Mechanical compression prophylaxis as an adjuvant to pharmacological prophylaxis reduced the risk of DVT by 50% (RR=0.50, 95% CI: 0.35 to 0.72, 13 studies) (Figure 24, Appendix E). There was no significant difference when mechanical prophylaxis was a adjuvant to another mechanical and a pharmacological prophylaxis (RR=1.22, 95% CI: 0.37 to 4.01, two studies).There was no significant heterogeneity between the subgroups ($\chi^2$ on 2 df =3.59; P=0.17)

**Effect on pulmonary embolism**: Overall, mechanical compression prophylaxis as an adjuvant reduced the risk of pulmonary embolism by 59% (RR=0.41, 95% CI: 0.27 to 0.63, 11 studies). Mechanical compression prophylaxis as an adjuvant to pharmacological prophylaxis reduced the risk of pulmonary embolism by 60% (RR=0.40, 95% CI: 0.25 to 0.62, six studies). There was no significant difference when mechanical compression was used as an adjuvant to another mechanical prophylaxis (RR=0.51, 95% CI: 0.05 to 5.43, two studies). (Figure 25, Appendix E). There was no significant difference when mechanical prophylaxis was a adjuvant to another mechanical and a pharmacological prophylaxis (RR=1.01, 95% CI: 0.06 to 16.05, one study).There was no significant heterogeneity between the subgroups ($\chi^2$ on 2 df =0.45; P=0.8).

**Effect on proximal DVT:** Overall, mechanical compression devices as an adjuvant reduced the risk of proximal DVT by 63% (RR=0.37, CI 0.23 to 0.61, 14 studies). Mechanical compression devices as an adjuvant to another mechanical prophylaxis reduced the risk of proximal DVT by 84% (RR=0.16, CI 0.06 to 0.42, five studies). There was no significant difference when mechanical compression devices were used as an adjuvant to pharmacological prophylaxis (RR=0.92, CI 0.41 to 2.07, five studies). (Figure 26, Appendix E). There was no significant heterogeneity between the subgroups ($\chi^2$ on 2 df =4.96; P=0.08).

### 5.5.3 Mechanical vs no prophylaxis and mechanical as an adjuvant combined

We combined 53 studies with a total of 8766 participants comparing mechanical prophylaxis with no prophylaxis and mechanical as an adjuvant to determine the overall effect of all mechanical compression methods.

**Effect on DVT:** Mechanical compression prophylaxis alone and mechanical as an adjuvant reduced the risk of DVT by 51% (RR=0.49, 95% CI: 0.41 to 0.58, 49 studies) (Figure 38, Appendix E). There was no statistically significant heterogeneity between the subgroups ($\chi^2$ on 3 df =7.12; P=0.07).

**Effect on pulmonary embolism**: Mechanical compression prophylaxis alone and mechanical as an adjuvant reduced the risk of pulmonary embolism by 51% (RR=0.49, 95% CI: 0.34 to 0.70, 21 studies) (Figure 39, Appendix E). There was no statistically significant heterogeneity between the subgroups ($\chi^2$ on 3 df =2.58; P=0.46).

**Effect on proximal DVT:** Mechanical compression prophylaxis alone and mechanical as an adjuvant reduced the risk of proximal DVT by 53% (RR=0.47, CI 0.36 to 0.61, 26 studies) (Figure 40, Appendix E). There was no statistically significant heterogeneity between the subgroups ($\chi^2$ on 3 df =5.49; P=0.14).

## 5.6 Clinical evidence on electrical stimulation

We examined the evidence for the effectiveness of electrical stimulation compared to using no prophylaxis, and compared to mechanical compression devices.

### 5.6.1 Electrical stimulation vs no prophylaxis

We identified two RCTs with 297 participants comparing electrical stimulation with no prophylaxis[83,336] (Evidence table 22, Appendix D). In one study, each patient was their own control and only one leg was given the electrical stimulation[83].

**Effect on DVT:** Electrical stimulation produced a 59% reduction in the risk of DVT compared to no prophylaxis (RR=0.41, 95%CI: 0.23 to 0.73) (Figure 34, Appendix E).

**Effect on pulmonary embolism:** Only one study reported pulmonary embolism. There was no evidence that electrical stimulation reduced the incidence of PE (RR=0.36, 95% CI: 0.12 to 1.07) (Figure 35, Appendix E).

**Effect on proximal DVT:** One study reported proximal DVT. There were no events in either arm.[83].

### 5.6.2 Electrical stimulation vs intermittent pneumatic compression plus graduated compression stockings

We identified one study[397] with 150 patients that compared electrical stimulation with a combination of intra-operative and post-operative use of IPC devices and graduated compression stockings (Evidence table 21, Appendix D). Electrical calf stimulation was begun after induction of anaesthesia and continued for the duration of surgery only. The study did not report pulmonary embolisms or major bleeding rates. A third arm received unfractionated heparin and is reported in the section on mechanical vs pharmacological interventions.

**Effect on DVT:** The combination of IPC device and stockings significantly reduced the risk of DVT compared to electrical stimulation by 80% (RR=0.20, 95% CI 0.05-0.77) (Figure 36, Appendix E).

**Effect on proximal DVT:** There was no significant difference between groups (RR=0.19, 95% CI 0.01 – 4.10) (Figure 37, Appendix E).

## *5.7 Patient views and concordance with mechanical interventions*

We identified two studies of graduated compression stockings, one in orthopaedic patients[42] and the other in mixed surgical patients[32] (Evidence table 23, Appendix D).

The first study investigated the effect of graduated compression stockings on venous haemodynamics in an RCT of orthopaedic patients[42]. Eighty patients wore thigh length stockings and 80 wore knee length. After 1 hour of wear significantly more patients in the thigh length group had wrinkles in their stockings and reported discomfort. Half of the patients in each group felt unable to manage the stockings independently. Knee and thigh length stockings were similarly efficient in reducing venous stasis, the main outcome of the study.

The second study was a survey carried out on 16 wards over one day to see if the hospital policy of wearing thigh length stockings was practiced[32]. A total of 218 patients on mixed-specialty surgical wards were surveyed. Ninety-nine (46%) of the patients were wearing stockings. Nine of the 14 patients (64%) wearing above knee stockings wore them correctly. Those not wearing them correctly wore them rolled down to below the knee. Seventy-seven of the 85 patients (91%) wearing below knee stockings wore them correctly. Overall, only 4% (nine of 218 patients surveyed) wore graduated compression stockings in accordance with hospital policy.

One study tried a new IPC device applied to either the calf or foot of 30 patients having elective joint replacement[532]. Twenty three of the 27 patients who gave feedback found the device either 'comfortable' or 'very comfortable'. Three patients who had reported discomfort or sleep disturbance had been allocated to the foot garment. All 20 nurses asked to rate the system rated the device 'highly positively'.

One study that looked at foot impulse devices[562] measured the time patients spent wearing a pulsatile pneumatic plantar compression (PlexiPluse) foot wrap after knee arthroplasty surgery, and determined patients' and nurses' views of the device (Evidence table 23, Appendix D). The device was worn for 79.8% of the actual time possible (1314/1646 hours) between 9am to 5pm. Patients found the device "moderately comfortable" to "very comfortable" and "easy to wear", the pumping action "slightly comfortable", and generally, they thought the pump reduced swelling. Nurses found it easy to use and comfortable for their patients.

We identified two studies that compared mechanical interventions (Evidence table 23, Appendix D). In one study, intermittent pneumatic compression devices plus graduated compression stockings were compared with foot pumps in hip joint replacement patients[443]. Some of the participants also had warfarin or heparin given at the discretion of the surgeon. The foot pump was worn for more hours per day over 4 days postoperatively, although the result was not significant. Significantly more patients were

"comfortable" or had no complaints with the foot pump (85/120) than in the group with the sequential compression device and stockings (57/104). Thirty-five participants in the foot pump group were having revision surgery and had previously used a sequential device. Twenty-four out of the 35 preferred the foot pump, seven of the 35 preferred sequential compression and four had no preference.

The second study[576] was an RCT that compared the use of pneumatic foot wraps (Plexi-Pulse) with sequential pneumatic compression wraps (Kendall) in adults undergoing major thoracolumbar reconstructive spinal procedures. All participants also wore thigh length stockings. The devices were worn continuously, starting postoperatively and continuing until ambulatory, and then worn when in bed until discharge. There was a wide range of responses in both groups ranging from extremely comfortable to extremely uncomfortable. There was no difference in visual analogue scores for comfort between the two groups.

## 5.8 Economic evidence on mechanical interventions

We found seven studies (Evidence table 65, Appendix D). The studies evaluated either intermittent pneumatic compression (IPC) or graduated compression stockings (GCS). All were decision models. Surgery type was heterogeneous (orthopaedic, general, gynaecological and urological). There was only one UK-based study (the others were mainly from USA plus Canada & South Africa). They mainly estimated health gain in terms of lives saved not QALYs. Most studies included the cost of prophylaxis, diagnosis and treatment of DVT/PE. However, they did not include long-term prophylaxis or treatment of post-thrombotic syndrome.

### 5.8.1 IPCD vs no prophylaxis

Three model-based studies found that IPCD was dominant (health improving and cost *saving*). Three model-based studies found that IPCD increased costs but was cost-effective[253,347,356,410,411,433].

### 5.8.2 Stockings vs no prophylaxis

Three model-based studies found that the use of stockings was the dominant strategy[410,411,433].

### 5.8.3 Stockings adjunctive to heparin

Four model-based studies found that adjunctive use of stockings was cost-effective[3,410,411].

### 5.8.4 Stockings vs IPC devices

One model found that stockings dominated. Another that IPC devices dominated and a third found that IPC devices were more effective but the cost-effectiveness was indeterminable[410,411,433].

### 5.8.5 Stockings adjunctive to IPC devices

One model found that the use of stockings was cost-effective when used as an adjunct to IPC devices[411].

## 5.9 Conclusions on clinical and cost effectiveness of mechanical interventions

Mechanical methods of thromboprophylaxis are effective at reducing the risk of DVT and appear to have broadly similar effects irrespective of whether they are used alone or in conjunction with a pharmacological method. Overall, the evidence indicated that mechanical methods reduced the risk of PE and of proximal venous thrombosis, but owing to the potential for selective reporting of only the more promising of trial results on such outcomes, the precise size of such effects could not be determined reliably. In subgroup analysis we found no evidence of differences in the effectiveness of different types of mechanical thromboprophylaxis.

There were no cost-effectiveness studies evaluating foot impulse devices or electrical stimulation. There were seven decision models evaluating the cost-effectiveness of stockings or intermittent compression devices. They consistently found that mechanical compression methods were cost-effective compared with no prophylaxis. There was inconsistency in the results with regard to comparisons between stockings and intermittent pneumatic compression. The most important contribution to this heterogeneity is the methods of estimating effectiveness. The trials employed to estimate effectiveness varied and sometimes crude methods of indirect comparison were used to estimate the event rates for each strategy. To ensure that all of the good quality clinical evidence is used systematically, we have conducted our own mixed treatment comparison meta-analysis and cost-effectiveness analysis (chapters 12 & 13).

The GDG, after taking into account the results of the direct comparisons (this chapter), the mixed treatment meta-analysis, the economic model (chapters 12 and 13) and patient views, recommend the use of graduated compression stockings because they can be used during surgery, on the ward after surgery and at home after discharge (please see chapters 12 and 13 for further details of the analysis). Stockings are

suitable for most patients, however, the GDG recommend that they should not be used by patients with peripheral arterial disease. Thigh length stockings are recommended in preference to knee length as there is evidence that they are more effective, but the GDG recognise that there may be cases where thigh-length stockings are not suitable, due to fit or patient comfort. In such cases knee length stockings should be used as an alternative. The compression profile should be 18mmHg at the ankle, 14mmHg at the knee and 8mmHg at the upper thigh. An ankle pressure of 18mmHg is consistent with class II British Standard and class I European Standard.

Given that immobility is considered to be a cause or risk factor for VTE (see chapter 4), providing prophylaxis until a patient is back to their usual level of mobility was considered good practice by the GDG. They should be informed that doing this will reduce their risk of developing venous thromboembolism.

Few studies were available that investigated patients' views and concordance with using mechanical interventions. Those that were showed: thigh-length stockings were less comfortable and more likely to be worn incorrectly (that is, rolled down to the knee) than knee-length stockings; patients had no preference between foot wraps and intermittent pneumatic compression devices and one study showed a preference for foot pumps over intermittent pneumatic compression devices. The GDG decided that it was good practice that patients using stockings should be shown how to wear them correctly and staff trained in the use of the product should monitor their use and provide assistance if they are not being worn correctly.

The GDG also recommend IPC and foot impulse devices can be used as an alternative to compression stockings whilst in hospital. This was because the evidence did not indicate that there was a difference in the effectiveness between these mechanical compression devices (sections 5.4 and 5.5) and the GDG wanted to give flexibility to clinicians to decide on the most suitable method for each patient. When used, these should be worn for as much of the time as is possible and practical while the patient is in bed or sitting in a chair.

## 5.10 *Recommendations*

**Inpatients having surgery should be offered thigh-length graduated compression/anti-embolism stockings from the time of admission to hospital unless contraindicated (for example, in patients with established peripheral arterial disease or diabetic neuropathy). If thigh-length stockings are inappropriate for a particular patient for reasons of compliance or fit, knee-length stockings may be used as a suitable alternative.**

**The stocking compression profile should be equivalent to the Sigel profile, and approximately 18 mmHg at the ankle, 14 mmHg at the mid-calf and 8 mmHg at the upper thigh.**

**Healthcare professionals should encourage patients to wear their graduated compression/anti-embolism stockings until they return to their usual level of mobility. Patients should be informed that this will reduce their risk of developing VTE.**

**Patients using graduated compression/anti-embolism stockings should be shown how to wear them correctly by staff trained in the use of that product. Stocking use should be monitored and assistance provided if they are not being worn correctly.**

**Intermittent pneumatic compression or foot impulse devices may be used as alternatives or in addition to graduated compression/anti-embolism stockings while surgical patients are in hospital.**

**When used on the ward, intermittent pneumatic compression or foot impulse devices should be used for as much of the time as is possible and practical while the patient is in bed or sitting in a chair.**

## 5.11 Recommendation for research

### 5.11.1 Research Question

What is the effectiveness of graduated compression/anti-embolism stockings and either an intermittent pneumatic compression (IPC) device or a foot pump device, compared with graduated compression/anti-embolism stockings alone, in reducing the risk of (objectively diagnosed) DVT and/or PE in adult inpatients undergoing surgery? Patients may be risk of VTE because of the procedure (e.g. hip fracture), or because they have risk factors for such disease (e.g. thrombophilia, age over 60 years).

All patients should be screened for the presence of DVT and/or PE.

Randomisation would be stratified into two groups:

- Patients in whom pharmacological prophylaxis is contraindicated (e.g. because of an increased risk of bleeding).

- Patients in whom pharmacological prophylaxis is indicated, but the risk of VTE is very high.

Secondary outcomes would be costs, quality of life, skin problems, myocardial infarction, stroke and other adverse events e.g. bleeding.

### 5.11.2 Why this research is important

Only a small number of RCTs have evaluated a combination of mechanical methods. These studies have shown promising results, but have involved small numbers of patients, and the large effect sizes observed in some of these studies suggest bias.

This trial would inform the management of two specific groups of patients in whom the available treatment options are restricted.

- Patients at high risk of VTE who cannot have heparin because they are also at increased risk of bleeding.
- Patients at very high risk of VTE who can be given pharmacological prophylaxis who might benefit from combination mechanical thromboprophylaxis.

This trial would help extend the current NICE recommendations. There may be cost savings if the addition of a second mechanical method results in further reduction of VTE.

The proposed research is feasible but depends on the extent to which surgeons are certain about the value of combining two mechanical methods of thromboprophylaxis, because this would determine their willingness to randomise. Before any trial this issue would need to be explored in detail, possibly via a questionnaire.

# 6 Pharmacological methods of prophylaxis

## 6.1 Introduction

The pharmacological methods of prophylaxis considered within this guideline are oral anticoagulants, dextran, fondaparinux, heparins (unfractionated and low molecular weight heparin), aspirin and danaparoid. This chapter reports evidence on the effectiveness of pharmacological prophylaxis compared to nil (or placebo) or to any other pharmacological methods. The effectiveness of pharmacological prophylaxes when compared to mechanical methods is reported in chapter 7.

## 6.2 Oral anticoagulants (OAC)

### 6.2.1 Introduction

Warfarin is a coumarin derivative and acts as a vitamin K antagonist.

The synthesis of active clotting factors II, VII, IX and XI (as well as the anticoagulant proteins C and S) requires carboxylation of glutamic acid residues which is dependent on the presence of vitamin K. Antagonism of vitamin K therefore reduces the amount of these factors, thereby producing a state of anticoagulation.

Warfarin can be administered as a 'fixed', lower dose which is intended to never achieve anticoagulation to a degree that represents sufficient hazard of bleeding to require monitoring. It is more usually given at adjusted, variable doses to achieve a therapeutic level, as estimated by attaining an INR (International Normalised Ratio) of 2-3. This requires frequent monitoring and takes approximately 5 days for a stable antithrombotic effect to be achieved. There is much variability in responses to warfarin, which is determined by several factors including age, genetic status, medications, diet and medical conditions. The most important complication of anticoagulation is bleeding but, if required, the effect of warfarin can be reversed with vitamin K, prothrombin concentrates and replenishment of clotting factors by the use of fresh frozen plasma.

### 6.2.2 Clinical evidence on oral anticoagulants

#### 6.2.2.1 Oral anticoagulants vs no prophylaxis

We identified two systematic reviews, one with nine RCTs[444] and one with an additional two RCTs[374] (Evidence Table 24, Appendix D). Overall, a total of 1320 participants were included.

**Effect on DVT:** Oral anticoagulants reduced the risk of DVT by 51% (RR=0.49, 95% CI: 0.34 to 0.73, ten studies) (Figure 41, Appendix E). There was significant heterogeneity within the results ($\chi^2$ on 9 df = 25.55, p=0.002).

**Effect on pulmonary embolism:** Oral anticoagulants reduced the risk of PE by 82% (RR=0.18, 95% CI: 0.08 to 0.45, five studies) (Figure 42, Appendix E).

**Effect on proximal DVT:** Oral anticoagulants reduced the risk of proximal DVT by 58% (RR=0.42, 95% CI: 0.22 to 0.78, four studies) (Figure 43, Appendix E).

**Effect on major bleeding:** Oral anticoagulants increased the risk of bleeding by 58% (RR=1.58, 95% CI: 1.01 to 2.47, nine studies) (Figure 44, Appendix E).

#### 6.2.2.2 Oral anticoagulants as an adjuvant intervention

We identified one systematic review with five RCTs[444] and a total of 688 participants (Evidence Table 25, Appendix D). Two studies used graduated compression stockings as background therapy, one used intermittent pneumatic compression devices, one used unfractionated heparin and one used dextran.

**Effect on DVT:** There was no significant difference in DVT when OACs were used as an adjuvant. (RR=0.64, 95% CI: 0.39 to 1.06, four studies) (Figure 45, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference for OAC when used as an adjuvant intervention (RR=0.42, 95% CI: 0.10 to 1.75, three studies) (Figure 46, Appendix E).

**Effect on proximal DVT:** There was no significant difference for OAC when used as an adjuvant intervention (RR=0.70, 95% CI: 0.28 to 1.73, two studies) (Figure 47, Appendix E).

**Effect on major bleeding:** There was no significant difference in major bleeding events when OACs were used as an adjuvant intervention (RR=2.84, 95% CI: 0.57 to 14.19, three studies) (Figure 48, Appendix E).

#### 6.2.2.3 Adjusted vs fixed (lower) dose oral anticoagulants

We identified one systematic review with two RCTs[444] and one additional RCT[59] that compared adjusted dose oral anticoagulants with fixed dose in a total of 567 participants (Evidence Table 26, Appendix D). The adjusted dose studies all gave the first dose preoperatively and continued the regimen for between three days and six weeks postoperatively. The fixed dose regimens were all started preoperatively and continued for between 14 days and 6 weeks postoperatively.

**Effect on DVT:** Adjusted-dose OAC reduced the risk of DVT by 49% (RR=0.51, 95% CI: 0.30 to 0.85, three studies) compared to fixed dose OAC (Figure 49, Appendix E). This result was determined almost entirely by the results of one study[158].

**Effect on pulmonary embolism:** Two studies reported PE rates. Only one event was observed (RR=2.97, 95% CI: 0.12 to 72.01) (Figure 50, Appendix E).

**Effect on proximal DVT:** There was no significant difference between adjusted and fixed dose oral anticoagulants (RR=0.36, 95% CI: 0.12 to 1.09, one study) (Figure 51, Appendix E).

**Effect on major bleeding:** There was no significant difference between adjusted and fixed dose OAC (RR=1.22, 95% CI: 0.47 to 3.18, two studies) (Figure 52, Appendix E).

#### 6.2.2.4 Timing of initiation of oral anticoagulants

We identified two studies[167,509] with 321 participants that compared timing of initiation of OAC (Evidence Table 27, Appendix D). In one study[167], patients were randomised to receive warfarin started 10-14 days preoperatively or the night before surgery. In the second study, patients received acenocoumarol begun either four days preoperatively or on the night before surgery.

**Effect on DVT:** No significant difference was found between treatment regimens (RR=1.04, CI: 0.73 to 1.48, one study) (Figure 53, Appendix E).

**Effect on PE:** One study reported PE data but the effect was not estimable as no events were reported (Figure 54, Appendix E).

**Effect on proximal DVT:** No significant difference was found between treatment regimens (RR=0.98, CI: 0.53 to 1.79, one study) (Figure 55, Appendix E).

**Effect on major bleeding:** There was no significant difference (RR=2.55, CI: 0.51 to 12.84, one study) (Figure 56, Appendix E).

#### 6.2.2.5 Duration of OAC prophylaxis

One study looked at the effectiveness of extending OAC prophylaxis beyond discharge[429] (Evidence Table 28, Appendix D). 360 patients received OAC while hospitalised and were randomised at discharge to either continue OAC for a further 4 weeks or to stop prophylaxis. The study assessed proximal DVT only; hence the effect on all DVT (i.e. including thromboses in the calf) was not estimable.

**Effect on pulmonary embolism:** There was no significant difference when extending prophylaxis beyond discharge (RR=0.32, 95% CI: 0.01 to 7.78) (Figure 57, Appendix E).

**Effect on proximal DVT:** Extending prophylaxis beyond discharge reduced the risk of proximal DVT by 88% (RR=0.12, 95% CI: 0.02 – 0.95) (Figure 58, Appendix E).

**Effect on major bleeding:** Only one bleeding event was observed, in the extended prophylaxis group (RR=2.87, 95% CI: 0.12 to 69.99) (Figure 59, Appendix E).

#### 6.2.2.6 OAC vs unfractionated heparin

We identified two systematic reviews[374,444] and one additional RCT[535] with a total of 730 participants from six RCTs (Evidence Table 29, Appendix D).

**Effect on DVT:** Oral anticoagulants increased the risk of DVT by 54% compared to unfractionated heparin (RR=1.54, 95% CI: 1.12 to 2.12, six studies) (Figure 60, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference between OACs and unfractionated heparin (RR=1.80, 95% CI: 0.63 to 5.14, one study) (Figure 61, Appendix E).

**Effect on proximal DVT:** There was no significant difference between interventions (RR=8.31, 95% CI: 0.45 to 155.00, one study) (Figure 62, Appendix E).

**Effect on major bleeding:** There was no significant difference between OACs and unfractionated heparin (RR=0.55, 95% CI: 0.24 to 1.23, four studies) (Figure 63, Appendix E).

### 6.2.2.7 OAC vs low molecular weight heparin

We identified two systematic reviews[374,444] and one additional RCT[109] with a total of 11,560 participants from 11 RCTs (Evidence Table 30, Appendix D).

**Effect on DVT:** LMWH significantly reduced the risk of DVT compared to OAC (RR=1.43, 95% CI: 1.31 to 1.56, nine studies) (Figure 64, Appendix E). The results were heterogeneous ($\chi^2$ on 9 df = 19.13, p=0.02). Sensitivity analyses suggested that this was due to the inclusion of Hull et al 1993[252].

**Effect on pulmonary embolism:** There was no significant difference (RR=1.52, 95% CI: 0.66 to 3.48, seven studies) (Figure 65, Appendix E).

**Effect on proximal DVT:** LMWH signicantly reduced the risk of proximal DVT compared to OAC (RR=1.23, 95% CI: 1.01 to 1.50, nine studies) (Figure 66, Appendix E).

**Effect on major bleeding:** There was no significant difference between oral anticoagulants and LMWH (RR=0.80, 95% CI: 0.51 to 1.24, 10 studies) (Figure 67, Appendix E).

### 6.2.2.8 OAC vs aspirin

We identified four RCTs with a total of 902 participants[216,339,428,577] (Evidence Table 31, Appendix D). In one study all patients also received intermittent pneumatic compression devices and graduated compression stockings[577]. Oral anticoagulants were started preoperatively in three studies and postoperatively in one study. Aspirin was started at admission or preoperatively for three studies and postoperatively in one study. The duration of both regimens was until discharge in three studies and not reported for one study.

**Effect on DVT:** The difference between OAC and aspirin was not significant (RR=0.65, 95% CI: 0.41 to 1.04, three studies) (Figure 68, Appendix E). There was heterogeneity with the results ($\chi^2$ on 2 df = 6.01, p=0.05), the cause of which could not be determined.

**Effect on pulmonary embolism:** There was no significant difference found between OAC and aspirin (RR=0.77, CI: 0.39 to 1.51, three studies) (Figure 69, Appendix E).

**Effect on proximal DVT:** There was no significant difference between OAC and aspirin (RR=0.87, CI: 0.57 to 1.35, four studies) (Figure 70, Appendix E).

**Effect on major bleeding:** There was no significant difference between groups (RR=5.08, 95% CI: 0.61 to 42.28, one study) (Figure 71, Appendix E).

### 6.2.2.9 OAC vs dextran

We identified one systematic review[374] and two additional RCTs[216,316] with a total of 990 participants from 6 RCTs (Evidence Table 32, Appendix D).

**Effect on DVT:** There was no significant difference between OAC and dextran (RR=0.91, 95% CI: 0.53 to1.56, five studies) (Figure 72, Appendix E). There was heterogeneity within the results ($\chi^2$ on 4 df = 13.82, p=0.008) caused by the inclusion of one study[165] which used dextran 40 (the other studies used dextran 70). This study found a significant benefit of OAC over dextran 40 (RR=0.40, 95% CI: 0.22 to 0.75), whereas the difference was not significant for OAC vs dextran 70 (RR=1.24, 95% CI: 0.69 to 2.23, four studies).

**Effect on pulmonary embolism:** There was no significant difference between dextran and OAC (RR=0.50, 95% CI: 0.22 to 1.13, four studies) (Figure 73, Appendix E).

**Effect on proximal DVT:** OAC reduced the risk of proximal DVT by 71% compared to dextran (RR=0.27, 95% CI: 0.10 to 0.78, two studies) (Figure 74, Appendix E).

**Effect on major bleeding:** It was not possible to obtain a reliable estimate of effect due to the low number of events observed (RR=3.78, 95% CI: 0.68 to 21.04, two studies) (Figure 75, Appendix E).

#### 6.2.2.10 OAC vs danaparoid

We identified one systematic review with two RCTs with a total of 777 participants[374] (Evidence Table 33, Appendix D).

**Effect on DVT:** There were significantly more DVT in the OAC group compared to the danaparoid group (RR=2.14, 95% CI: 1.53 to 2.99, two studies) (Figure 76, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference found between OAC and danaparoid (RR=3.03, 95% CI: 0.32 to 28.94, two studies) (Figure 77, Appendix E).

**Effect on proximal DVT:** There was no significant difference found between OAC and danaparoid (RR=2.69, 95% CI: 0.73 to 10.01, one study) (Figure 78, Appendix E).

**Effect on major bleeding:** There was no significant difference found between OAC and danaparoid (RR=0.79, 95% CI: 0.38 to 1.67, two studies) (Figure 79, Appendix E).

#### 6.2.2.11 Patient views on oral anticoagulants

No studies were identified that examined patient views on oral anticoagulants as a prophylaxis.

### 6.2.3 Economic evidence on oral anticoagulants

#### 6.2.3.1 The studies

We included 17 studies evaluating the cost-effectiveness of OAC (14 models, two RCTs and one cohort study) (Evidence Table 65, Appendix D). All studies were for major orthopaedic surgery. The studies were based in Europe or North America; none were based in the UK and mainly estimated health gain in terms of VTEs averted or deaths averted. All studies included the cost of prophylaxis, diagnosis and treatment of DVT/PE. Most included the cost of bleeding. One included the cost and quality of life impact associated with post-thrombotic syndrome.

#### 6.2.3.2 OAC vs no prophylaxis

Five model-based studies found that OAC was dominant (health improving and cost *saving*)[378,391,410,456].

#### 6.2.3.3 OAC prophylaxis extended beyond discharge

One model-based study found that extended use dominated standard in-hospital use[467].

#### 6.2.3.4 OAC vs danaparoid

There was one model[378]. In this model danaparoid dominates OAC.

#### 6.2.3.5 OAC vs dextran

Two studies found that OAC was dominant[378,456].

#### 6.2.3.6 OAC vs aspirin

One cohort study found that OAC was more effective but cost-effectiveness is indeterminable[12].

#### 6.2.3.7 OAC vs aspirin (extended beyond discharge)

One model-based study found that OAC was more effective but cost-effectiveness is indeterminable[467].

#### 6.2.3.8 OAC vs UFH

Three model-based studies[3,378,410]and one cohort study[12] found that OAC dominated UFH. These results are contradicted by our clinical review (above) that found UFH to be more effective.

#### 6.2.3.9 OAC vs LMWH

There were two RCT-based studies[169,259] and 10 models[3,75,91,122,223,368,391,402,546]. LMWH was dominant in four studies. LMWH was cost-effective in four studies. OAC was dominant in two studies and in two studies cost-effectiveness was indeterminable.

#### 6.2.3.10 OAC vs LMWH (extended beyond discharge)

One model-based study found that OAC dominated LMWH for elective hip patients[547]. A second model-based study found that LMWH was cost-effective in the same group of patients[176]

### 6.2.4 Conclusions of clinical and cost effectiveness on oral anticoagulants

Oral anticoagulants (OACs) are effective in reducing DVT and PE but significantly increase the risk of major bleeding. Adjusted dose OACs (i.e. monitoring INR levels) are significantly more effective than lower fixed doses in reducing the risk

of DVT. There was not enough evidence to determine differences in effect for major bleeding.

For reducing the risk of DVT, OACs are more effective than dextran 40 but less effective than unfractionated or low molecular weight heparins and danaparoid. There was no evidence of a difference for aspirin or dextran 70. There was not enough evidence to determine a difference in major bleeding between OACs and other pharmacological prophylaxes.

There were a number of studies evaluating the cost-effectiveness of OAC. They consistently found that OAC was cost-effective compared with no prophylaxis. There was great inconsistency in the results with regard to comparisons with other types of pharmacological prophylaxis including LMWH. The most important contribution to this heterogeneity is the methods of estimating effectiveness. The trials employed to estimate effectiveness varied and sometimes crude methods of indirect comparison were used to estimate the event rates for each strategy. To ensure that all of the good quality clinical evidence is used systematically, we have conducted our own mixed-treatment comparison meta-analysis and cost-effectiveness analysis (Chapters 12 and 13).

## 6.3 Danaparoid

### 6.3.1 Introduction

Danaparoid is a mixture of low molecular weight sulphated glycosamino-glycans. It acts in a similar way to heparin and pentasaccharides as above and reduces the risk of VTEs by binding to antithrombin, leading to anti Xa activity. Danaparoid is administered subcutaneously either continuously or twice daily usually 1-4 hours pre-operatively. It is normally used when the patient has had HIT, because the antibody against heparin does not cross-react with it.

#### 6.3.1.1 Clinical evidence on danaparoid

Evidence comparing danaparoid with oral anticoagulants can be found in the section on oral anticoagulants.

#### 6.3.1.2 Danaparoid vs no prophylaxis

We identified one RCT that compared danaparoid with a placebo[239] and had 196 participants (Evidence Table 34, Appendix D). Major bleeding was not reported.

**Effect on DVT:** Danaparoid reduced the risk of DVT by 73% (RR=0.27, 95% CI: 0.17 to 0.45, one study) (Figure 80, Appendix E).

**Effect on pulmonary embolism:** There were no events in either arm and therefore the effect on PE could not be estimated (Figure 81, Appendix E).

**Effect on proximal DVT:** Danaparoid reduced the risk of proximal DVT by 67% (RR=0.33, 95% CI: 0.16 to 0.69, one study) (Figure 82, Appendix E).

#### 6.3.1.3 Danaparoid vs dextran

We identified one RCT that compared danaparoid with dextran 70 with 247 participants (Evidence Table 35, Appendix D) BERGQVIST1991. The study did not report the number of proximal DVT or major bleeding events.

**Effect on DVT:** Danaparoid reduced the risk of DVT by 62% compared to dextran (RR=0.38, 95% CI: 0.22 to 0.65, one study) (Figure 83, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference between the groups (RR=0.56, 95% CI: 0.05 to 6.05, one study) (Figure 84, Appendix E).

#### 6.3.1.4 Danaparoid vs low molecular weight heparin

We identified one RCT that compared danaparoid with two types of low molecular weight heparin[45] with a total of 197 participants (Evidence Table 36, Appendix D). There was no difference in effectiveness between the two low molecular weight heparins and the results for these groups were combined in the meta-analysis.

**Effect on DVT:** There was no significant difference in effectiveness between danaparoid and LMWH (RR=0.47, 95% CI: 0.14 to 1.59, one study) (Figure 85, Appendix E).

**Effect on pulmonary embolism:** There were no event rates in either group and therefore the effect on PE was not estimable (Figure 86, Appendix E).

**Effect on proximal DVT:** There was no significant difference in effectiveness between danaparoid and LMWH (RR=0.82, 95% CI: 0.16 to 4.10, one study) (Figure 87, Appendix E).

**Effect on major bleeding:** Event rates observed in the study were low and no significant difference was found (RR=0.68, 95% CI: 0.07 to 6.38, one study) (Figure 88, Appendix E).

#### 6.3.1.5 Danaparoid vs unfractionated heparin

We identified two RCTs that compared danaparoid with unfractionated heparin. In one study danaparoid was compared with unfractionated heparin alone[181] (Evidence Table 37, Appendix D). In the other, danaparoid was compared with unfractionated heparin plus dihydoergotamine[333]. There were a total of 822 participants. Neither study reported major bleeding events.

**Effect on DVT:** Danaparoid reduced the risk of DVT by 39% compared to unfractionated heparin (RR=0.61, 95% CI: 0.45 to 0.84, two studies) (Figure 89, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference between danaparoid and unfractionated heparin (RR=1.65, 95% CI: 0.22 to 12.33, two studies) (Figure 90, Appendix E).

**Effect on proximal DVT:** There was no significant difference between danaparoid and unfractionated heparin (RR=0.75, 95% CI: 0.29 to 1.95, one study) (Figure 91, Appendix E).

#### 6.3.1.6 Danaparoid vs aspirin

We identified one RCT that compared danaparoid with aspirin[190] with 251 participants (Evidence Table 38, Appendix D). The study did not report major bleeding events.

**Effect on DVT:** Danaparoid reduced the risk of DVT by 36% compared to aspirin (RR=0.64, 95% CI: 0.43 to 0.97, one study) (Figure 92, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference between danaparoid and aspirin on the effect of PE (RR=0.34, 95% CI: 0.01 to 8.17, one study) (Figure 93, Appendix E).

**Effect on proximal DVT:** There was no significant difference between danaparoid and aspirin (RR=0.51, 95% CI: 0.20 to 1.33, one study) (Figure 94, Appendix E).

#### 6.3.1.7 Patient views of this group of interventions

No studies were identified examining patient views on danaparoid as a prophylaxis.

### 6.3.2 Economic evidence on danaparoid

#### 6.3.2.1 The studies

We identified three decision models[378,545,546] (Evidence Table 65, Appendix D), all of which were for major orthopaedic surgery. One study was conducted in Netherlands and the other two were from USA.

The studies estimated health gain in terms of VTEs averted or death averted. All studies included the cost of prophylaxis, diagnosis and treatment of DVT/PE. None of the studies considered HRQL of post-thrombotic syndrome and the cost of bleeding event.

#### 6.3.2.2 Danaparoid vs nil

There was one model[378]. In this model danaparoid dominates.

#### 6.3.2.3 Danaparoid vs LMWH

There were three models[378,545,546]. In two models danaparoid dominates, in the third model LMWH dominates

#### 6.3.2.4 Danaparoid vs UFH

There was one model[378]. In this model danaparoid dominates.

#### 6.3.2.5 Danaparoid vs dextran

There was one model[378]. In this model danaparoid dominates.

### 6.3.3 Conclusions on clinical and cost effectiveness of danaparoid

Danaparoid is effective in reducing DVT. Danaparoid is more effective for reducing the risk of DVT than dextran, aspirin and unfractionated heparin. Based on the results of one study, danaparoid is as effective as low molecular weight heparin. There was no evidence for fondaparinux and there was not enough evidence to conclude on major bleeding for any comparison.

There were a few studies evaluating the cost-effectiveness of danaparoid. Danaparoid appears to be cost-effective compared with no prophylaxis. There were contradictory results compared with LMWH. The most important contribution to this heterogeneity is the method of estimating effectiveness. The trials employed to estimate effectiveness varied and sometimes crude methods of indirect comparison were used to estimate the event rates for each strategy. To ensure that all of the good quality clinical evidence is used

systematically, we have conducted our own mixed-treatment comparison meta-analysis and cost-effectiveness analysis (Chapters 12 and 13).

## 6.4 Dextran

### 6.4.1 Introduction

Dextran works by binding onto red cells and platelets and thus reducing their adhesiveness. It also has a heparin-like activity that requires the presence of antithrombin. It is available as preparations with different molecular weights (e.g. Dextran 10, 40 ,60 and 70) in different dilutions, the larger ones being excreted poorly by the kidneys and can therefore retain their antithrombotic effect for long periods.(days). Dextrans are administered intravenously and need large volumes (greater than 1.5l) to achieve a concentration which will have anticoagulant effect. The practicalities of administering it mean that it is generally used during operative period only. There are few side effects but it can cause anaphylaxis (severe allergic reactions), fluid overload and renal failure and can interfere with the interpretation of blood group testing by causing clumping of red cells.

### 6.4.2 Clinical evidence for dextran

The evidence for dextran compared to oral anticoagulants is reported in the previous section.

#### 6.4.2.1 Dextran vs no prophylaxis

We identified a systematic review of 13 RCTs[444] and two additional studies[69,500], giving a total of 15 studies with 1944 participants (Evidence Table 39, Appendix D). The majority of the studies were carried out before 1983 with only two carried out in the 1990s.

**Effect on DVT:** Dextran reduced the risk of DVT by 28% (RR=0.72, 95% CI: 0.55 to 0.95, 15 studies). There was significant heterogeneity within the results ($\chi^2$ on 14 df = 29.73, p=0.008) (Figure 95, Appendix E).

**Effect on pulmonary embolism:** The results were not significantly different between the groups (RR=0.76, 95% CI: 0.33 to 1.77, two studies) (Figure 96, Appendix E).

**Effect on proximal DVT:** There was no significant difference between dextran and no prophylaxis (RR=0.73, 95% CI: 0.42 to 1.25, six studies) (Figure 97, Appendix E).

**Effect on major bleeding:** Five studies assessed major bleeding rates. No events were observed in either arm across all of the trials and the effects of dextran on major bleeding were therefore not estimable (Figure 98, Appendix E).

#### 6.4.2.2 Effectiveness of dextran as an adjuvant intervention

We identified one systematic review of five RCTs[444] and two additional studies[69,500] giving a total of seven studies with 672 participants (Evidence Table 40, Appendix D).

**Effect on DVT:** Dextran reduced the risk of DVT by 42% (RR=0.58, 95% CI: 0.44 to 0.76, five studies) when used an adjuvant therapy (Figure 99, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference between groups when dextran was used as an adjuvant (RR=0.50, 95% CI: 0.22 to 1.14, three studies) (Figure 100, Appendix E).

**Effect on proximal DVT:** There was no significant difference between groups (RR=0.69, 95% CI: 0.39 to 1.24, one study) (Figure 101, Appendix E).

**Effect on major bleeding:** When used as an adjuvant dextran increased major bleeding events by 138% (RR=2.38, 95% CI: 1.13 to 4.98, three studies) (Figure 102, Appendix E).

#### 6.4.2.3 Subgroup analysis of dextran vs no prophylaxis studies: Effectiveness of different molecular weights of dextran

The studies identified used different molecular weights of dextran. Three studies used dextran 40[204,228,249], ten used dextran 70[49,52,69,93,267,346,500,543,560], one used mixed weights (40 and 70)[262] and one study did not report the molecular weight[153]. We carried out a subgroup analysis of the dextran vs nil studies to look for a difference in effect between dextran 40 and dextran 70. Subgroup analyses were not possible for pulmonary embolism (there were no studies evaluating dextran 40 that reported PE) or major bleeding (there were no events in any of the trials).

**Effect on DVT:** Neither dextran 40 or dextran 70 significantly reduced the risk of DVT when compared to no prophylaxis (dextran 40 RR=0.71, 95% CI: 0.50 to 1.01, three studies; dextran 70 RR=0.67, 95% CI 0.44 to 1.03, ten studies). There was heterogeneity within the dextran 70 results ($\chi^2$ on 9 df = 23.96, p=0.004). The subgroup analysis

found no significant difference in the magnitude of effect for dextrans 40 or 70 ($\chi^2$ on 1 df = 0.18, p=0.67) (Figure 103, Appendix E).

**Effect on proximal DVT:** When analysed separately, nether dextran 40 (RR=0.29, 95% CI: 0.05 to 1.83, two studies) or dextran 70 (RR=0.96, 95% CI: 0.52 to 1.76, four studies) significantly reduced the risk of proximal DVT. The subgroup analysis found no significant difference in the magnitude of effect for dextrans 40 or 70 ($\chi^2$ on 1 df = 1.62, p=0.2) (Figure 104, Appendix E).

#### 6.4.2.4 Comparison of dextran with low molecular weight heparin

We identified one review of five studies with a total of 1135 participants[444] (Evidence Table 41, Appendix D).

**Effect on DVT:** The dextran group had significantly more DVT events than LMWH (RR=1.79, 95% CI: 1.22 to 2.63, five studies) (Figure 105, Appendix E). There was significant heterogeneity ($\chi^2$ on 4 df = 10.08, p=0.04) within the results, which appeared to be due to one study[565] although no specific cause could be identified.

**Effect on pulmonary embolism:** Due to low event rates the difference in effect was not significant (RR=1.20, 95% CI: 0.41 to 3.54, four studies) (Figure 106, Appendix E).

**Effect on proximal DVT:** There was no significant difference between dextran and LMWH (RR=1.30, 95% CI: 0.57 to 2.94, five studies) (Figure 107, Appendix E).

**Effect on major bleeding:** Four studies reported major bleeds. There were no events in either arm of any of the trials hence the relative risk of bleeding was not estimable (Figure 108, Appendix E).

#### 6.4.2.5 Comparison of dextran with unfractionated heparin

We identified one review of 10 RCTs[444] and we identified three more[30,171,360] giving a total of 13 studies with 1844 participants (Evidence Table 42, Appendix D).

**Effect on DVT:** There was no significant difference between dextran and unfractionated heparin (RR=1.32, 95% CI: 0.94 to 1.85, 13 studies) (Figure 109, Appendix E). There was considerable heterogeneity within the results ($\chi^2$ on 12 df = 32. 20, p=0.001).

**Effect on pulmonary embolism:** No significant difference was found between dextran and unfractionated heparin (RR=0.98, 95% CI: 0.59 to 1.62, five studies) (Figure 110, Appendix E). The result was almost entirely determined by one study[171].

**Effect on proximal DVT:** There was no significant difference between dextran and unfractionated heparin (RR=1.92, 95% CI: 0.89 to 4.15, five studies) (Figure 111, Appendix E).

**Effect on major bleeding:** There was no significant difference in risk of major bleeding for dextran or unfractionated heparin (RR=0.41, 95% CI: 0.15 to 1.18, eight studies) (Figure 112, Appendix E).

#### 6.4.2.6 Comparison of dextran with aspirin

One study of 187 participants compared low molecular weight dextran with aspirin[216] (Evidence Table 43, Appendix D).

**Effect on DVT:** There was no significant difference between dextran and aspirin (RR=0.64, 95% CI: 0.35 to 1.16) (Figure 113, Appendix E).

**Effect on proximal DVT:** There was no significant difference between dextran and aspirin (RR=0.66, 95% CI: 0.28 to 1.54) (Figure 114, Appendix E).

#### 6.4.2.7 Patient views on dextran

We did not identify any studies investigating patient views on dextran as a method of prophylaxis.

### 6.4.3 Economic evidence on dextran

#### 6.4.3.1 The studies

We identified three simple models (Evidence Table 65, Appendix D). All three looked at major orthopaedic surgery and one considered general surgery as well. There were no UK-based studies (one USA, one Netherlands, and one Denmark). They measured health outcome in terms of deaths averted or VTEs averted. Only one study measured the costs of treating bleeding and none considered recurrence or post-thrombotic syndrome.

#### 6.4.3.2 Dextran vs no prophylaxis

Two studies found that dextran was dominant (health improving and cost *saving*)[378,456].

#### 6.4.3.3 *Dextran vs UFH*

One study found that UFH was dominant and one found dextran was dominant[378,456].

#### 6.4.3.4 Dextran vs LMWH

Two studies found that LMWH was dominant[72,378].

### 6.4.4 Conclusions on clinical and cost effectiveness of dextran

Dextran is effective in reducing DVT. Dextran is not more effective than any other pharmacological method of prophylaxis in reducing the risk of DVT. Unfractionated and low molecular weight heparins are more effective for reduction of DVT risk. There was not enough evidence to conclude on major bleeding for any comparison.

There were only three studies evaluating the cost-effectiveness of dextran. They found that dextran is cost-effective compared with no prophylaxis. There was inconsistency in the results with regard to comparisons with other types of pharmacological prophylaxis including UFH. The most important contribution to this heterogeneity is the method of estimating effectiveness. The trials employed to estimate effectiveness varied and sometimes crude methods of indirect comparison were used to estimate the event rates for each strategy. To ensure that all of the good quality clinical evidence is used systematically, we have conducted our own mixed-treatment comparison meta-analysis and cost-effectiveness analysis (Chapters 12 and 13).

## 6.5 Heparins

### 6.5.1 Introduction

Natural heparin is a mixture of mucopolysaccharides of differing chain lengths and hence molecular sizes. Such 'unfractionated' pharmaceutical heparin (UFH) consists of chains of molecular weights from 5000 to over 40,000 Da (average 20,000 Da). Heparin acts as an anticoagulant by binding and accelerating the action of antithrombin, a naturally occurring inhibitor of thrombin and other coagulation enzymes (X, IX, XI and XII).

By distinctly different processes of fractionating or depolymerisation of natural heparin, several preparations of low molecular weight heparins (LMWH) are produced. Thus, although they are dissimilar in physical, chemical and biological properties, they consist of short chains of polysaccharides with an average molecular weight 3000 Da. They bind less avidly to other heparin binding proteins in the blood and are therefore more biologically available at lower doses and have more predictable levels. Both unfractionated and low molecular weight heparins can be administered intravenously (boluses and continuous) or by subcutaneous injections (twice to three times for UFH, once to twice daily for LMWH).

In addition to the outcomes for venous thromboembolism and major bleeding, we also considered heparin-induced thrombocytopenia (HIT). Few trials reported this is outcome, we have reported it when available.

### 6.5.2 Clinical evidence on heparins

The evidence for heparins compared to oral anticoagulants, danaparoid, and dextran can be found in preceding sections, the evidence for fondaparinux follows this section.

#### 6.5.2.1 Unfractionated heparin vs no prophylaxis

We identified one systematic review[108] and five additional RCTs[29,39,99,104,298] giving a total of 75 studies with 16,215 participants (Evidence Table 44, Appendix D). Additional background prophylaxis was also used in some studies: eight used graduated compression stockings, two used aspirin, two used intermittent pneumatic compression devices and one used dextran.

**Effect on DVT:** Unfractionated heparin reduced the risk of DVT by 56% compared to no prophylaxis (RR=0.44, 95% CI: 0.37 to 0.52, 61 studies) (Figure 115, Appendix E). There was significant heterogeneity within the results, the cause of which could not be determined ($\chi^2$ on 60 df = 129.45, p<0.00001).

**Effect on pulmonary embolism:** Unfractionated heparin reduced the risk of pulmonary embolism by 30% (RR=0.70, 95% CI: 0.53 to 0.93, 22 studies) (Figure 116, Appendix E).

**Effect on proximal DVT:** Unfractionated heparin reduced the risk of proximal DVT by 55% (RR=0.45, 95% CI: 0.34 to 0.60, 23 studies) (Figure 117, Appendix E).

**Effect on major bleeding:** Unfractionated heparin increased the risk of major bleeding by 46% (RR=1.46, 95% CI: 1.18 to 1.82, 59 studies) (Figure 118, Appendix E).

#### 6.5.2.2 Unfractionated heparin dose studies

We identified one study comparing a higher dose of UFH with a lower dose[88] with 100 participants (Evidence Table 45, Appendix D). One group of

patients was given 7500 IU twice daily whilst the other was given 5000IU twice daily. Proximal DVT and pulmonary embolism were not reported

**Effect on DVT:** There was no difference in DVT with 11 events in each group.

**Effect on major bleeding:** There were no major bleed events.

### 6.5.2.3 Low molecular weight heparin vs no prophylaxis

We identified three systematic reviews[264,373,587] and three additional RCTs[44,369,574] giving a total of 28 studies with 8935 participants (Evidence Table 46, Appendix D). In seven studies graduated compression stockings were given to all participants and in one study patients were allowed intraoperative dextran.

**Effect on DVT:** LMWH reduced the risk of DVT by 51% (RR=0.49, 95% CI: 0.44 to 0.56, 25 studies) (Figure 119, Appendix E).

**Effect on pulmonary embolism:** LMWH reduced the risk of pulmonary embolism by 64% (RR=0.36, 95% CI: 0.19 to 0.70, 13 studies) (Figure 120, Appendix E).

**Effect on proximal DVT:** LMWH reduced the risk of proximal DVT by 62% (RR=0.38, 95% CI: 0.26 to 0.56, 14 studies). There was significant heterogeneity within the results, the cause of which could not be determined ($\chi^2$ on 13 df = 24.24, p=0.03) (Figure 121, Appendix E).

**Effect on major bleeding:** LMWH increased the risk of major bleeding by 77% (RR=1.77, 95% CI: 1.28 to 2.46, 20 studies) (Figure 122, Appendix E).

We carried out a subgroup analysis, grouping studies according to whether background prophylaxis was used, to look for differences in effectiveness of heparin between these two conditions. The only significant difference in magnitude of effect between study groups was for proximal DVT ($\chi^2$ on 1 df = 6.22, p = 0.013). There was no significant difference for DVT, PE or major bleeding.

### 6.5.2.4 Pre- vs postoperative initiation of LMWH prophylaxis

We identified one study that compared LMWH begun 12 hours preoperatively with LMWH begun 12 hours postoperatively[413] (Evidence Table 47, Appendix D). Both groups received LMWH for 14 days or until discharge. After surgery, all patients underwent early mobilisation, elastic bandaging of the legs or graduated compression stockings, and physical exercise.

**Effect on DVT:** There was no significant difference between the groups (RR=1.14, 95% CI: 0.74 to 1.76) (Figure 123, Appendix E).

**Effect on pulmonary embolism:** There were no events for pulmonary embolism in either arm (Figure 124, Appendix E).

**Effect on proximal DVT:** There was no significant difference between the groups (RR=1.78, 95% CI: 0.55 to 5.78) (Figure 125, Appendix E).

**Effect on major bleeding:** There was no significant difference between the groups (RR=0.66, 95% CI: 0.11 to 3.85) (Figure 126, Appendix E).

### 6.5.2.5 Subgroup analysis of LMWH vs no prophylaxis studies: timing of initiation

We carried out a subgroup analysis of the low molecular weight heparin vs no prophylaxis studies to look for differences in the magnitude of effect according to whether heparin was begun pre- or postoperatively. Fifteen studies started LMWH preoperatively and nine studies began prophylaxis postoperatively.

**Effect on DVT:** LWMH begun preoperatively reduced the risk of DVT by 49% (RR=0.51, 95% CI: 0.44 to 0.60, 15 studies) compared to 53% when begun postoperatively (RR=0.47, 95% CI: 0.39 to 0.57, nine studies). There was no significant difference in the magnitude of these effects ($\chi^2$ on 1 df = 0.76, p=0.38) (Figure 127, Appendix E).

**Effect on pulmonary embolism:** LWMH begun preoperatively reduced the risk of pulmonary embolism by 79% (RR=0.30, 95% CI: 0.14 to 0.64, 10 studies). There was no significant difference when begun postoperatively (RR=0.76, 95% CI: 0.17 to 3.37, four studies). There was no significant difference in the magnitude of these effects ($\chi^2$ on 1 df = 1.01, p=0.31) (Figure 128, Appendix E).

**Effect on proximal DVT:** Preoperatively commenced LMWH reduced the risk of proximal DVT by 53% (RR=0.47, 95% CI: 0.30 to 0.74, eight studies). LMWH started postoperatively reduced risk by 72% (RR=0.28, 95% CI: 0.14 to 0.54, six studies) (Figure 129, Appendix E). There was no significant difference in the magnitude of

effects (chi-squared on 1 df = 3.06, p=0.08) (Figure 129, Appendix E).

**Effect on major bleeding:** LMWH begun preoperatively increased the risk of bleeding by 96% (RR=1.96, 95% CI: 1.35 to 2.84, 11 studies) (Figure 130, Appendix E). The results were chiefly determined by one study[416]. There was no significant difference between groups when LMWH was begun postoperatively (RR=1.23, 95% CI: 0.61 to 2.47, 9 studies) (Figure 130, Appendix E). There was no significant difference in the magnitude of effects for studies commencing LMWH preoperatively and those beginning prophylaxis postoperatively (chi-squared on 1 df = 1.37, p=0.24).

### 6.5.2.6 Low molecular weight heparin dose studies

We identified five studies comparing a higher dose of LMWH with a lower dose[7,46,112,220,495] with 3628 participants (Evidence Table 48, Appendix D). In two studies 30mg given twice daily was compared to 40mg given once. The remaining three studies compared the following doses: 5000 IU with 3000 IU, 5000 IU with 2500 IU and 3500 IU with 2500 IU.

**Effect on DVT:** A higher dose of LWMH reduced the risk of DVT by 45% (RR=0.55, 95% CI: 0.44 to 0.69, five studies) compared to the lower dose (Figure 131, Appendix E).

**Effect on pulmonary embolism:** Only one study reported PE rates and there were no events in either arm (Figure 132, Appendix E).

**Effect on proximal DVT:** There was no significant difference between higher or lower doses of LMWH (RR=0.86, 95% CI: 0.45 to 1.65, three studies) (Figure 133, Appendix E).

**Effect on major bleeding:** Lower dose LMWH had significantly less major bleeds than a higher dose (RR=2.44, 95% CI: 1.31 to 4.55, four studies) (Figure 134, Appendix E).

### 6.5.2.7 Subgroup analysis of LMWH vs no prophylaxis studies: dose

A subgroup analysis was carried out of the studies comparing low molecular weight heparin vs no prophylaxis to look for differences in the magnitude of effect according to dose. We grouped the studies into low (six studies) medium (eight studies) and high (13 studies) dose. None of the results showed significant heterogeneity.

**Effect on DVT:** Each of the categories of dose had a similar relative risk reduction for DVT (Low dose: RR=0.52, 95% CI: 0.42 to 0.64; medium dose: RR=0.48, 95% CI: 0.39 to 0.59; high dose: RR=0.49, 95% CI: 0.40 to 0.60) (Figure 135, Appendix E). There was no significant difference in the magnitude of these effects ($\chi^2$ on 2 df = 1.34, p=0.51).

**Effect on pulmonary embolism:** There was no significant difference between the groups (Low dose: RR=0.36, 95% CI: 0.11 to 1.12; medium dose: RR=0.26, 95% CI: 0.09 to 0.72; high dose: RR=0.74, 95% CI: 0.17 to 3.28) (Figure 136, Appendix E). There was no significant difference in the magnitude of these effects ($\chi^2$ on 2 df = 1.17, p=0.56).

**Effect on proximal DVT:** A higher dose appears to have a greater reduction in events than medium or lower doses (79% compared 63% and 43% respectively). (Low dose: RR=0.57, 95% CI: 0.37 to 0.88; medium dose: RR=0.37, 95% CI: 0.21 to 0.67; high dose: RR=0.21, 95% CI: 0.07 to 0.60) (Figure 137, Appendix E). However, there was no significant difference in the magnitude of these effects ($\chi^2$ on 2 df = 3.27, p=0.19).

**Effect on major bleeding:** There does not appear to be a difference in the results. (Low dose: RR=1.87, 95% CI: 1.28 to 2.74; medium dose: RR=1.42, 95% CI: 0.51 to 4.01; high dose: RR=1.56, 95% CI: 0.68 to 3.57) (Figure 138, Appendix E). There was no significant difference in the magnitude of these effects ($\chi^2$ on 2 df = 0.91, p=0.63).

### 6.5.2.8 Extending heparin prophylaxis beyond discharge

We identified one systematic review[256] and six additional studies[43,232,301,318,348,516] giving a total of 12 RCTs with 2809 participants (Evidence Table 49, Appendix D). In the intervention arm heparin was given for 7 days after discharge or between 19 and 30 days. In the control arm heparin was given until discharge or for six to 14 days.

**Effect on DVT:** Heparin reduced the risk of DVT by 52% (RR=0.48, 95% CI: 0.39 to 0.58, 11 studies) compared to nil in the post-discharge period (Figure 139, Appendix E).

**Effect on pulmonary embolism:** Continuing heparin reduced the risk of PE post-discharge by 66% (RR=0.34, 95% CI: 0.13 to 0.89, nine studies) (Figure 140, Appendix E).

**Effect on proximal DVT:** Heparin reduced the risk of proximal DVT post-discharge by 66%

(RR=0.34, 95% CI: 0.25 to 0.48, ten studies) (Figure 138, Appendix E).

**Effect on major bleeding:** Three studies reported major bleeding rates. In two studies there were no events in either arm (Figure 142, Appendix E). There was no significant difference in major bleeding events between groups (RR=1.23, 95% CI: 0.33 to 4.55).

#### 6.5.2.9 Low molecular weight vs unfractionated heparin

We identified two systematic reviews[300,373] and 16 additional RCTs[25,38,113,155,157,193,245,281,322,328,345,364,415,482,544,550] giving at total of 76 RCTs with 22,574 participants. We also identified on RCT that looked at fatal pulmonary embolism in 23,078 patients[206]. (Evidence Table 50, Appendix D).

**Effect on DVT:** Low molecular weight heparin reduced the risk of DVT by 13% (RR=0.87, 95% CI: 0.79 to 0.95, 67 studies) compared to unfractionated heparin (Figure 143, Appendix E).

**Effect on pulmonary embolism:** LMWH reduced the risk of PE by 34% compared to unfractionated heparin (RR=0.66, 95% CI: 0.46 to 0.95, 37 studies) (Figure 144, Appendix E).

**Effect on fatal pulmonary embolism**: One study[206] reported fatal PE confirmed by autopsy. The autopsy rate was 70.2% for this study. There was no significant difference between the groups (p=0.87).

**Effect on proximal DVT:** LMWH reduced the risk of proximal DVT by 39% (RR=0.62, 95% CI: 0.49 to 0.78, 19 studies) compared to unfractionated heparin (Figure 145, Appendix E).

**Effect on major bleeding:** LMWH reduced the risk of major bleeding by 14% (RR=0.87, 95% CI: 0.76 to 1.01, 47 studies) compared to unfractionated heparin (Figure 146, Appendix E).

**Effect on thrombocytopenia:** Two studies[206,345] reported on the incidence of thrombocytopenia but found no statistical difference between the groups.

#### 6.5.2.10 Patient views for heparins

Two prospective studies looked at self-injection of low molecular weight heparin in orthopaedic patients (Evidence Table 51, Appendix D). One was in total hip or knee replacement patients[110] the other in knee arthroplasty patients[493].

Colwell et al[110] evaluated postoperative self-injection of low molecular weight heparin for 21 days in 50 total hip or knee replacement patients. Patients were given instructions and a demonstration by the staff nurses, written and video instructional materials were also given on discharge. Follow up telephone interviews were conducted once per week and each patient was given a self-report injection diary to complete. Of the 40 who completed the trial, 22 were fully concordant, 15 were partially concordant and three did not manage to stick to the regimen. An assessment of patients showed that 49 out of 50 understood the importance of self administering heparin, 34 out of 50 felt comfortable giving injections. Generally, patients were happy with the level of information received regarding self-medication and felt that the syringe was relatively easy to use. Sixteen reported mild burning or stinging at the injection site and one reported mild bruising. The authors thought that concordance with the regimen might be higher in this study than in a normal population due to the follow up phone calls to check how patients were coping.

Spahn et al[493] evaluated postoperative self-injection of low molecular weight heparin for around 10 days in knee replacement patients. Patients were free to choose whether heparin injection was self-administered or given by a family member or a nursing service. Instructions on self injection were given by a physician or qualified nurse. All patients carried out their first and last injection in the presence of the instructor. They were also provided with an instruction booklet, elastic stockings and muscle and early mobilisation training. Assessment was carried out by anonymous questionnaire. Out of 300 patients 220 returned their questionnaires. Thirteen of these were incomplete leaving a possible 207. One hundred and sixty patients had elected to inject, 31 elected to have a family member inject them and the remaining 16 selected the nursing service. Fewer found it 'very unpleasant' in the self injection group than the family injection group or nursing injection group. Overall, prophylaxis was unsure in 54 out of 191 (28.3%) patients in the self or family member injection groups. Thirty-four out of 191 left out some injections and 25 out of 191 discontinued the injections early. Significantly more of those under 20 years old had unsure prophylaxis. Of those over 20 years old, 71.7% injected the required amount. Side effects had no influence on concordance with heparin use.

### 6.5.3 Economic evidence on heparins

Evidence on the cost-effectiveness of heparin compared with mechanical prophylaxis, OAC, dextran and fondaparinux has been reported in the respective sections.

#### 6.5.3.1 UFH vs no prophylaxis

We identified 10 models - five related to orthopaedic surgery, five general surgery and one gynaecological surgery (Evidence Table 65, Appendix D). Mainly they estimated health gain in terms of VTEs averted or deaths averted but one study estimated life-years. Four studies did not include cost of treating bleeding and none included post-thrombotic syndrome[3,141,253,347,356,378,391,410,433].

Six studies found UFH to be dominant, two found UFH to be cost-effective and one found that UFH was more effective but the cost-effectiveness was indeterminable.

#### 6.5.3.2 LMWH vs no prophylaxis

We identified eight models (Evidence Table 65, Appendix D) covering different types of surgery (Four orthopaedic, three general, one gynaecological)[3, 347, 356,378,391,433]. One study was from the UK (three USA, one South Africa and three Western Europe. They mainly estimated health gain in terms of VTEs averted or deaths averted but one study estimated the life-years gained. Two studies did not include the cost of bleeding; none included cost of post-thrombotic syndrome.

Three studies found that LMWH was dominant. Three found that it was cost-effective and in one study LMWH was more effective but the cost-effectiveness was indeterminable.

#### 6.5.3.3 LMWH as an adjuvant intervention

A model-based study[123] found that LMWH was cost-effective adjuvant to intermittent pneumatic compression in some onco-gynaecological surgery patients but not in those with poor prognosis (old age and late stage of disease).

#### 6.5.3.4 LMWH prophylaxis extended beyond discharge

We identified five decision analyses, one simple model[122,125,201,209,466,467] and one RCT[54] (Evidence Table 65, Appendix D). covering different kinds of surgery: five hip surgery, one knee surgery, one abdominal surgery and one general surgery.

Two studies were from the UK and five were from Switzerland.

Four studies estimated health gain in terms of VTEs averted or deaths averted, one measured life years gained, and two studies measured QALYs gained.

All studies included the cost of prophylaxis, diagnosis and treatment of DVT, PE and bleeding. One of the studies included the cost and health-related quality of life of post-thrombotic syndrome & recurrence.

In two studies of elective hip surgery patients, LMWH was dominant and in another LMWH was cost-effective. In one study LMWH is cost-effective for hip but not for knee surgery. In another study of elective hip surgery, LMWH was more effective but the cost-effectiveness was indeterminable.

In one study of general surgery patients and another of GI cancer patients, LMWH was not cost-effective.

#### 6.5.3.5 LMWH vs UFH

We identified 18 models[3,16,57,139,151,186,201,222,224,227,337,347,351,356,378,433,437,511] (Evidence Table 65, Appendix D) covering different types of surgery: orthopaedic (13 studies),general (11 studies), cardiac (one study) gynaecological (one study).

Three of these studies were conducted in UK.

The studies mainly estimated health gain in terms of VTEs averted or deaths averted. One study estimated Life Years and another study estimated Quality Adjusted Life Years.

All of the studies included the cost of prophylaxis, diagnosis and treatment of DVT/PE. Most of studies include the cost of bleeding. One study included cost and HRQL of post-thrombotic syndrome.

In 13 studies LMWH dominates, in three studies UFH dominates, in one study LMWH was cost-effective and in one studies the cost/effectiveness was indeterminable.

### 6.5.4 Conclusions on clinical and cost effectiveness of heparins

Unfractionated and low molecular weight heparins reduce the risk of DVT and PE, but increase the risk of major bleeding. For reducing the risk of DVT, unfractionated heparin is more effective than oral anticoagulants, dextran and aspirin, but less effective than danaparoid. Low molecular weight heparin is more effective than oral anticoagulants and dextran, but less effective than fondaparinux for preventing the risk of DVT. There is not enough evidence to conclude on major bleeding for any of these comparisons. Low molecular weight heparin shows a small but significant advantage over unfractionated heparin for all outcomes.

There was insufficient evidence to determine whether administration of LMWH should be initiated pre or post operatively. The GDG felt that research in this area was a priority and therefore decided to make a recommendation that further

research is carried out. This recommendation is discussed in more detail below (section 6.10).

There was inconclusive evidence on the dose of LMWH. Our direct comparison indicated a significant reduction in risk of DVT at high dose but also an increased risk of bleeding. Our subgroup analysis found no conclusive differences for any outcomes except proximal DVT. We therefore could not make recommendations for a specific dose of LMWH.

Extending LMWH beyond discharge reduces the risk of developing DVT in this period. A subgroup analysis suggests LMWH is as effective in reducing the risk of DVT whether started pre- or postoperatively. There was not enough evidence to examine differences in major bleeding for these comparisons.

There were a number of studies evaluating the cost-effectiveness of heparin. They consistently found that heparin was cost-effective compared with no prophylaxis. There was inconsistency in the results with regard to comparisons between the two types of heparin and evaluations of extended use. The most important contribution to this heterogeneity is the method of estimating effectiveness. The trials employed to estimate effectiveness varied and sometimes crude methods of indirect comparison were used to estimate the event rates for each strategy. To ensure that all of the good quality clinical evidence is used systematically, we have conducted our own mixed-treatment comparison meta-analysis and cost-effectiveness analysis (Chapters 12 and 13).

## 6.6 Fondaparinux

### 6.6.1 Introduction

Fondaparinux is a synthetic pentasaccharide, which is based on the antithrombin binding region of heparin in the body. It acts as a catalyst for the antithrombin inhibition of coagulation factor Xa. However, it does not directly inhibit thrombin, because this requires a minimum of 13 additional saccharide units which is present in unfractionated and LMW heparin. It is therefore a specific, indirect inhibitor of activated factor Xa through its potentiation of antithrombin. It is given subcutaneously postoperatively and administered once daily. .

### 6.6.2 Clinical evidence on fondaparinux

We found no studies comparing fondaparinux with oral anticoagulants or dextran.

#### 6.6.2.1 Fondaparinux vs low molecular weight heparin

We identified five RCTs comparing Fondaparinux with Low Molecular Weight Heparin (LMWH) (Evidence Table 52, Appendix D)[9,35,146,317,528]. Graduated compression stockings were worn by the majority of patients in three of the studies, by around half the patients in one study, and the final study did not give the number but stated that they were permitted.

**Effect on DVT:** Fondaparinux reduced the risk of DVT by 48% (RR=0.52, 95% CI: 0.44 to 0.60, five studies) compared to LMWH (Figure 147, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference between fondaparinux and LMWH (RR=1.23, 95% CI: 0.59 to 2.56, five studies) (Figure 148, Appendix E).

**Effect on proximal DVT:** There was no significant difference between fondaparinux and LMWH (RR=0.50, 95% CI: 0.24 to 1.05, five studies) (Figure 149, Appendix E). There was significant heterogeneity within the results ($\chi^2$ on 4 df = 13.51, p=0.009). This could be due to the variation in the initiation of LMWH.

**Effect on major bleeding:** Fondaparinux was associated with significantly more major bleeds than LMWH (RR=1.49, 95% CI: 1.16 to 1.92, five studies) (Figure 150, Appendix E).

#### 6.6.2.2 Duration of fondaparinux prophylaxis

One study looked at the effectiveness of extending prophylaxis with fondaparinux beyond discharge[147] (Evidence Table 53, Appendix D). In a multicentre trial, 656 patients received 2.5mg fondaparinux for 6–8 days after surgery (the use of graduated compression stockings was also permitted). They were then randomised to either continue receiving fondaparinux for a further 19–23 days or to stop prophylaxis.

**Effect on DVT:** Extending fondaparinux prophylaxis reduced the risk of DVT post-discharge by 96% (RR=0.04, 95% CI: 0.01 to 0.13, one study) (Figure 151, Appendix E).

**Effect on pulmonary embolism:** Continuing fondaparinux after discharge reduced the risk of PE by 89% (RR=0.11, 95% CI: 0.01 to 0.88, one study) (Figure 152, Appendix E).

**Effect on proximal DVT:** Fondaparinux reduced the risk of developing proximal DVT in the

post-discharge period by 94% (RR=0.06, 95% CI: 0.01 to 0.24, one study) (Figure 153, Appendix E).

**Effect on major bleeding:** There was no significant difference between fondaparinux and LMWH (RR=13.08, 95% CI: 0.74 to 231.23, one study) (Figure 154, Appendix E).

#### 6.6.2.3 Patient views of fondaparinux

We found no studies investigating patient views of Fondaparinux as a method of prophylaxis.

### 6.6.3 Economic evidence on fondaparinux

#### 6.6.3.1 The studies

We found 12 studies evaluating the cost-effectiveness of fondaparinux for patients undergoing major orthopaedic surgery (six models, four RCTs) (Evidence Table 65, Appendix D). Eleven studies compared fondaparinux with LMWH. One study compared the cost effectiveness of 1 week vs 1 month duration of Fondaparinux for patients undergoing either hip fracture or hip replacement surgery.

Eight studies were based on a single comprehensive model, which included costs and health effects associated with post-thrombotic syndrome. They varied in terms of parameter estimates, especially unit costs, which were from different countries (including one UK-based study)

The other four studies were all conducted by the same group of authors and each was based on a single RCT. These just looked at events occurring within the trial period.

#### 6.6.3.2 Fondaparinux vs LMWH

The eight model-based studies[21,64,138,196,221,343,505,507] showed fondaparinux to be cost saving over five years. In their 90 day results some studies found cost savings and the others found fondaparinux to be cost-effective.

In the trial-based studies[496,497,548,549], the results varied by type of surgery. For hip fracture fondaparinux was more effective but cost-effectiveness was indeterminable. For knee replacement fondaparinux was dominant. For hip replacement, one study favoured fondaparinux and the other favoured LMWH.

#### 6.6.3.3 Duration of fondaparinux

The only study found[62] showed fondaparinux at 1 month to be cost-effective respect to fondaparinux (one week) in terms of life year gained in both the models for patients with hip fracture and hip replacement at 30 days, while it is cost-*saving* at 5 years. These results have to be interpreted with caution since the study was undertaken in Switzerland where health care prices are much higher than in the UK NHS.

### 6.6.4 Conclusions of clinical and cost effectiveness of fondaparinux

Fondaparinux is more effective than low molecular weight heparin for reducing the risk of DVT and proximal DVT, however, it also significantly increases major bleeding. Extending fondaparinux beyond discharge reduces the risk of developing DVT and proximal DVT in this period without significantly increasing major bleeding.

In ten out of 11 studies fondaparinux was found to be cost-effective or cost saving compared with LMWH. There was still some variability in results due to the selection of RCTs and differences in treatment costs assumed. In one study the extended fondaparinux was found to be cost effective. To ensure that all of the good quality clinical evidence is used systematically, we have conducted our own mixed-treatment comparison meta-analysis and cost-effectiveness analysis (Chapters 12 and 13).

## 6.7 Aspirin

### 6.7.1 Introduction

Aspirin inhibits platelet function through its irreversible inhibition of the enzyme cyclo-oxygenase-1 (COX-1) and thereby blocking thromboxane A2 production. Thromboxane induces platelet aggregation (and vessel wall vasoconstriction) which are required for the clotting cascade and thrombus formation. This effect lasts for the duration of the platelet lifespan. However, although it may take 10 days for the entire platelet population to be renewed, haemostasis has been shown to be normal if 20% of them have normal COX activity.

### 6.7.2 Clinical evidence on aspirin

The evidence comparing aspirin with oral anticoagulants, dextran and fondaparinux can be found in preceding sections.

#### 6.7.2.1 Antiplatelet therapy vs no prophylaxis

We identified one systematic review that examined the effectiveness of antiplatelet therapy in reducing the risk of venous thrombosis[22] with 9089 participants (Evidence Table 54, Appendix D). Nine studies compared aspirin with no prophylaxis, 16 compared aspirin in combination with other

antiplatelet therapy with no prophylaxis and 17 compared other antiplatelet therapies. Some studies compared more than one regimen of antiplatelet therapy with no prophylaxis. The review also included nine studies investigating high risk medical patients but these were excluded as medical patients are not included in this guideline.

**Effect on DVT:** All antiplatelet therapies reduced the risk of DVT by 24% (RR=0.76, 95% CI: 0.65 to 0.87, 44 studies). Aspirin as a single prophylaxis reduced risk of DVT by 31% (RR=0.69, 95% CI: 0.48 to 0.97, nine studies). There was significant heterogeneity within the aspirin alone results ($\chi^2$ on 8 df = 23.91, p=0.002). (Figure 155, Appendix E).

**Effect on proximal DVT:** Antiplatelet therapies reduced the risk of proximal DVT by 39% (RR=0.61, 95% CI: 0.46 to 0.82, eleven studies). Aspirin as a single prophylaxis reduced the risk of proximal DVT by 56% (RR=0.44, 95% CI: 0.26 to 0.75, four studies). (Figure 156, Appendix E).

**Effect on major bleeding:** Most of the studies were small and had no events in either arm for major bleeding (Figure 157, Appendix E). There was no significant difference between antiplatelet therapies and no prophylaxis (RR=1.30, 95% CI: 0.67 to 2.52, 41 studies).

### 6.7.2.2 Aspirin as an adjuvant intervention

We identified one systematic review[22] with six studies and four extra studies[380,431,541,577] giving a total of ten RCTs that looked at aspirin as an adjuvant prophylaxis (Evidence Table 55, Appendix D). Five studies with 1374 participants compared aspirin plus unfractionated heparin with unfractionated heparin alone. Three studies with 137 participants compared aspirin plus dipyridamole with dipyridamole alone. One study with 148 participants compared aspirin plus IPC devices and GCS with IPC devices and GCS alone. The remaining study included two multicentre RCTs with 17,444 participants investigating aspirin on a background of different prophylaxes. The background prophylaxes were unfractionated heparin, low molecular weight heparin, graduated compression stockings, regional anaesthesia and non-steroidal anti-inflammatory drugs including aspirin not related to the trial.

**Effect on DVT:** There was no significant difference between aspirin plus heparin compared to heparin alone (RR=0.83, 95% CI: 0.59 to 1.17, four studies) or aspirin plus dipyridamole compared to dipyridamole alone (RR=0.63, 95% CI: 0.33 to 1.19, three studies). The other comparisons did not report DVT. (Figure 158, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference for aspirin as an adjuvant to unfractionated heparin (RR=1.02, 95% CI: 0.39 to 2.65, one study) and aspirin as an adjuvant to IPC devices plus GCS (RR=3.16, 95% CI: 0.13 to 76.44, one study). Aspirin adjuvant to a variety of additional prophylaxis reduced the risk of pulmonary embolism by 40% (RR=0.60, 95% CI: 0.43 to 0.84, two studies). (Figure 159, Appendix E).

**Effect on proximal DVT:** There was no significant difference in proximal DVT for any of the outcomes (aspirin as an adjuvant to unfractionated heparin - RR=0.63, 95% CI: 0.37 to 1.07, five studies; aspirin as an adjuvant to dipyridamole - RR=0.32, 95% CI: 0.01 to 7.63, one study; aspirin as an adjuvant to IPC devices and GCS (RR=0.82, 95% CI: 0.32 to 2.09, one study). (Figure 160, Appendix E).

**Effect on major bleeding:** Aspirin plus unfractionated heparin increased bleeding by 47% (RR=1.47, 95% CI: 1.09 to 1.99, five studies). There was no significant difference in major bleeding for the investigating aspirin as an adjuvant to a variety of additional prophylaxis (RR=1.09, 95% CI: 0.92 to 1.30, two studies). There were no events in the aspirin as an adjuvant to dipyridamole study. (Figure 161, Appendix E).

### 6.7.2.3 Higher dose aspirin vs lower dose

We identified one systematic review[22] that included three RCTs with 184 participants comparing a higher dose aspirin with a lower dose (Evidence Table 56, Appendix D). None of the comparisons used similar doses: one compared 3900mg with 975mg; another compared 1000mg with 250mg; and the third compared 1200 mg with 300mg.

**Effect on DVT:** There was no significant difference between doses of aspirin (RR=0.92, 95% CI: 0.65 to 1.30, three studies) (Figure 162, Appendix E).

**Effect on major bleeding:** Two studies reported major bleeding, one had no events and the other had one event in the lower dose arm (RR=0.29, 95% CI: 0.01 to 6.38) (Figure 163, Appendix E).

### 6.7.2.4 Aspirin vs unfractionated heparin

We identified six RCTs with 1174 participants that compared aspirin with unfractionated heparin (Evidence Table 57, Appendix D).

**Effect on DVT:** There were significantly more DVT events in the aspirin group compared to the unfractionated heparin group (RR=1.57, 95% CI: 1.02 to 2.40, five studies) (Figure 164, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference between aspirin and unfractionated heparin (RR=1.31, 95% CI: 0.37 to 4.66, two studies) (Figure 165, Appendix E).

**Effect on proximal DVT:** There was no significant difference between aspirin and unfractionated heparin (RR=1.64, 95% CI: 0.70 to 3.83, one study) (Figure 166, Appendix E).

**Effect on major bleeding:** There was no significant difference in event rates for major bleeds (RR=1, 95% CI: 0.20 to 4.93, three studies) (Figure 167, Appendix E).

#### 6.7.2.5 Patient views on aspirin

No studies were identified examining patient views on aspirin as a prophylaxis.

### 6.7.3 Economic evidence on aspirin

The cost-effectiveness of aspirin compared with OAC, has been reported earlier in this chapter.

#### 6.7.3.1 The studies

We identified two models[3,467] and one cohort study[12] (Evidence Table 65, Appendix D). All of the three studies were for major orthopaedic surgery. One of the studies was from Norway; one was from Switzerland and one from South Africa.

The health gain was estimated in terms of VTEs averted or death averted. All of the studies included the cost of prophylaxis, diagnosis and treatment of DVT/PE. Two of the studies included the cost of bleeding. None of the studies considered Health-related quality of life (HRQL) of post-thrombotic syndrome.

#### 6.7.3.2 Aspirin vs UFH

We identified one cohort study[12] and one model[3]. In one study aspirin dominates, while in the other UFH is more effective but the cost-effectiveness is indeterminable.

#### 6.7.3.3 Aspirin vs LMWH

We identified one model[3]. The LMWH result more effective but cost-effectiveness was indeterminable.

#### 6.7.3.4 Aspirin vs nil (post-discharge period)

We identified one model[467]. In this study aspirin dominates.

### 6.7.4 Conclusions of clinical and cost effectiveness on aspirin

Aspirin and all antiplatelet therapies reduced the risk of DVT compared to no prophylaxis. The studies also suggest an increase in the risk of major bleeding but there was not enough data to show a significant difference. Studies investigating aspirin as adjuvant to unfractionated heparin showed a non-significant reduction in risk of DVT and proximal DVT in the aspirin plus heparin arm, but also showed a significant increase in the risk of major bleeding. Aspirin as an adjuvant to a variety of background prophylaxis reduced the risk of pulmonary embolism in orthopaedic patients with a non-significant increase in major bleeding. There was little data to determine a difference between different aspirin doses. Unfractionated heparin was better in reducing the risk of DVT than aspirin. There was no difference in major bleeding rates.

There were only three studies evaluating the cost-effectiveness of aspirin and none compared aspirin with nil during the hospital stay. There was inconsistency in the cost-effectiveness results comparing aspirin with heparin. The most important contribution to this heterogeneity is the method of estimating effectiveness. The trials employed to estimate effectiveness varied and sometimes crude methods of indirect comparison were used to estimate the event rates for each strategy. To ensure that all of the good quality clinical evidence is used systematically, we have conducted our own mixed-treatment comparison meta-analysis and cost-effectiveness analysis (Chapters 12 and 13).

## 6.8 Conclusions for pharmacological prophylaxis

Pharmacological interventions are effective in reducing DVT. Data were not always available or there were not enough events to determine the effectiveness of pharmacological interventions in reducing proximal DVT and PE. Where data were available there was a tendency towards a reduction in these events. Comparisons between the methods of pharmacological prophylaxis are considered further in chapter 12.

Most studies excluded patients who were prescribed anticoagulation or antiplatelet therapy for other conditions such as heart disease. The GDG therefore recommend that clinicians should consider the risks and benefits of stopping this treatment prior to surgery.

## 6.9 Recommendations

**The risks and benefits of stopping pre-existing established anticoagulation or antiplatelet therapy before surgery should be considered.**

Further analysis of the direct evidence was performed using a mixed treatment comparison meta analysis (chapter 12). This data was incorporated into an economic model (chapter 13) allowing the cost effectiveness of different pharmacological methods to be compared. Recommendations on the most clinically and cost effective pharmacological strategies can be found in chapter 13.

## 6.10 Recommendation for research

The GDG identified that research would be valuable on the timing of administration of low molecular weight heparin.

### 6.10.1.1 Research Question

What is the effectiveness of LMWH started pre-operatively compared to LMWH started post-operatively in reducing the risk of (objectively diagnosed) DVT or PE in adult patients undergoing inpatient surgical procedures?

All patients should be screened for the presence of DVT and/or PE. Secondary outcomes of interest are costs, quality of life, other adverse events e.g. myocardial infarction, stroke, extracranial or intracranial bleeding.

### 6.10.1.2 Why this research is important

The currently available randomised evidence is too limited to determine whether giving LMWH can be safely delayed until after surgery, or whether it must be given pre-operatively. This guideline recommends that LMWH is used for many patients at high risk of VTE is therefore non-specific about timing. This is a major gap in the evidence.

Although there may be only small differences in safety and efficacy between these two strategies, a policy of giving LMWH post-operatively may reduce the time that patients need to be in hospital prior to surgery. It therefore might have major benefits for patients.

As there is uncertainty around this question, it should be possible to find surgeons willing to randomise between these 2 strategies. The principal practical difficulty with this randomised trial would be the need for a very large sample size (possibly >10,000 patients), since the likely differences in DVT/PE and bleeding rates are small.

# 7 Comparison of mechanical and pharmacological prophylaxis

## 7.1 Introduction

This chapter examines the various comparisons of mechanical and pharmacological prophylaxis. The pharmacological methods of prophylaxis considered within this guideline were oral anticoagulants, dextran, fondaparinux, heparins (unfractionated and low molecular weight heparin), aspirin and danaparoid.

Mechanical methods of prophylaxis are split into two groups: mechanical compression methods (graduated compression stockings, intermittent pneumatic compression devices and foot impulse devices) and electrical stimulation.

## 7.2 Clinical evidence on mechanical compression vs pharmacological interventions

### 7.2.1 Mechanical methods vs unfractionated heparin

We identified 10 RCTs with 1049 participants that compared a mechanical device with unfractionated heparin (Evidence Table 58, Appendix D). The mechanical device used was graduated compression stockings (GCS) in two studies[156,435]; intermittent pneumatic compression (IPC) device in studies[105,107,298,307,366] (with GCS given to both groups as a background therapy in one of these studies[366]); foot pump in one study (with GCS as a background therapy)[464]; IPC device plus GCS in one study[397]; and in one study patients in the mechanical group were randomised to receive either GCS or IPC device[214]. In two studies[214,366] dihydroergotamine was given in addition to unfractionated heparin.

**Effect on DVT:** There was no significant difference between mechanical devices and unfractionated heparin on the risk of DVT (RR=0.78, 95% CI: 0.44 to 1.38, 8 studies) (Figure 168, Appendix E). There was significant heterogeneity within the results ($\chi^2$ on 8 df = 16.27, p=0.04). This is possibly due to two of the sutdies including background therapy of stockings in both groups, Santori et al, 1994[464] and Mellbring et al, 1986[366]. Removing these from the analysis removes the heterogeneity.

**Effect on pulmonary embolism:** There was no significant difference between mechanical devices and unfractionated heparin in the risk of pulmonary embolism (RR=1, 95% CI: 0.22 to 4.45, three studies) (Figure 169, Appendix E).

**Effect on proximal DVT:** There was no significant difference in the risk of proximal DVT (RR=0.26, 95% CI: 0.03 to 2.29, three studies) (Figure 170, Appendix E).

**Effect on major bleeding:** One study reported major bleeding. There were no events in either arm therefore the effect on major bleeding could not be estimated (Figure 171, Appendix E).

### 7.2.2 Mechanical methods vs low molecular weight heparin

We identified seven studies with 925 participants that compared mechanical devices with low molecular weight heparin (Evidence Table 58, Appendix D). The mechanical device used was an IPC device in three studies[136,357,501] (two of these studies used GCS as background prophylaxis in both groups[136,357]), foot pump in three studies[66,553,554] and foot pump plus stockings in an IPC device plus graduated compression stockings in one study[399].

**Effect on DVT:** There was no difference between mechanical devices and low molecular weight heparin in the risk of DVT (RR=1.49, 95% CI: 0.95 to 2.33, 6 studies) (Figure 168, Appendix E).

**Effect on pulmonary embolism:** Four studies reported pulmonary embolism data (Figure 169, Appendix E). There was only one event reported

and therefore a reliable estimate of effect could not be obtained (RR=3.04, 95% CI: 0.13 to 74.07).

**Effect on proximal DVT:** There was no significant difference in proximal DVT (RR=1.58, 95% CI: 0.89 to 2.82, five studies) (Figure 170, Appendix E).

**Effect on major bleeding:** There was no significant difference in major bleeding. (RR=0.58, 95% CI: 0.13 to 2.57) (Figure 171, Appendix E).

### 7.2.3 Mechanical methods vs oral anticoagulants

We identified six studies with 788 participants that compared mechanical devices with oral anticoagulants (Evidence Table 58, Appendix D). The mechanical device used was an IPC device in five studies[27,96,166,275,412] and an IPC device plus graduated compression stockings in one study[446].

**Effect on DVT:** There was no difference between mechanical devices and oral anticoagulants on the risk of DVT (RR=0.83, CI: 0.49-1.41, six studies) (Figure 168, Appendix E).

**Effect on pulmonary embolism:** Three studies reported pulmonary embolism data, although no events were observed in two of these studies (Figure 169, Appendix E). There was no significant difference in the risk of pulmonary embolism (RR=5.63, 95% CI: 0.28 to 114.27).

**Effect on proximal DVT:** Oral anticoagulants were significantly more effective in reducing the risk of proximal DVT compared mechanical devices (RR=2.40, 95% CI: 1.28 to 4.48, three studies) (Figure 170, Appendix E).

**Effect on major bleeding:** Two studies recorded major bleeding events. No events were observed in either study.

### 7.2.4 Mechanical methods vs aspirin

We identified two studies with 174 participants comparing mechanical devices with aspirin[207,362] (Evidence Table 58, Appendix D). The mechanical devices evaluated were intermittent pneumatic compression device in both studies. We identified no studies comparing aspirin with any other mechanical device. In one study[362] patients were randomised to receive either a high or a low dose (1300 mg and 325 mg respectively, both three times daily). We combined the results for the aspirin groups for the purpose of the meta-analysis. In the other study[207] the results were reported separately for patients having unilateral and bilateral knee replacements. This has been treated as two separate studies in the analysis.

**Effect on DVT:** Mechanical prophylaxis reduced the risk of DVT by 41% compared to aspirin (RR=0.59, 95% CI: 0.40 to 0.88, three studies) (Figure 168, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference in the risk of PE (RR=1.37, 95% CI: 0.35 to 5.35, three studies) (Figure 169, Appendix E).

**Effect on proximal DVT:** There was no significant difference on the risk of proximal DVT (RR=0.75, 95% CI: 0.14 to 3.92, three studies) (Figure 170, Appendix E).

**Effect on major bleeding:** One study reported major bleeding. One event was observed in the group receiving aspirin. The difference was not significant (RR=0.67, 95% CI: 0.03 to 15.06) (Figure 171, Appendix E).

### 7.2.5 Mechanical methods vs dextran

We found one study with 192 participants that compared a mechanical device (intermittent pneumatic compression) with dextrans[489] (Evidence Table 58, Appendix D). Patients in the pneumatic compression group wore the device during surgery only. Patients in the dextran group received prophylaxis at the induction of anaesthesia and within 8 hours of completing the surgery. The study reported outcomes for deep vein thrombosis only; hence the effects on proximal DVT, pulmonary embolism and major bleeding could not be estimated.

**Effect on DVT:** Dextrans were more effective in reducing the risk of DVT compared to mechanical prophylaxis (RR=1.75, 95% CI: 1.11 to 2.77, 1 study) (Figure 168, Appendix E).

### 7.2.6 Mechanical methods vs fondaparinux

We did not identify any studies that compared mechanical devices with fondaparinux.

### 7.2.7 Mechanical methods vs danaparoid

We did not identify any studies that compared mechanical devices with danaparoid.

### 7.2.8 Mechanical methods vs unfractionated heparin and aspirin

We identified one study with 25 patients comparing foot pumps with unfractionated heparin and aspirin[498] (Evidence Table 58, Appendix D). Only DVT was reported as an outcome.

**Effect on DVT:** There was no significant difference in the risk of DVT (RR=0.09, 95% CI: 0.01 to 1.56) (Figure 168, Appendix E).

### 7.2.9 Other comparisons

We identified two studies that did not fit into any of the categories mentioned above. Eskander et al, 1997[149] compared using IPC from time of admission for 48 hours then LMWH with LMWH used for the whole period. There was no significant difference for DVT, pulmonary embolism, proximal DVT or major bleeding between the groups (Evidence Table 58, Appendix D). Pitto et al, 2004[420] compared using LMWH during the operation followed by foot impulse device postoperatively with the use of LMWH for the whole period. There was no significant difference for DVT, pulmonary embolism, proximal DVT or major bleeding between the groups (Evidence Table 58, Appendix D).

## 7.3 Clinical evidence on electrical stimulation vs pharmacological interventions

### 7.3.1 Electrical stimulation vs dextran

We identified one study with 103 participants that compared electrical calf stimulation with dextran (Evidence Table 22, Appendix D). Proximal DVT and major bleeding events were not reported[336].

**Effect on DVT:** There was no significant difference in the risk of DVT (RR=0.68, 95% CI: 0.24 to 1.93) (Figure 172, Appendix E).

**Effect on pulmonary embolism:** There was no significant difference in the risk of pulmonary embolism (RR=1.42, 95% CI: 0.44 to 4.61) (Figure 173, Appendix E).

### 7.3.2 Electrical stimulation vs unfractionated heparin

We identified one study with 100 participants comparing electrical calf stimulation with unfractionated heparin[397] (Evidence Table 21, Appendix D). Electrical stimulation was delivered during the surgery only whilst unfractionated heparin was begun preoperatively and continued until discharge. The study did not report pulmonary embolism or major bleeding events.

**Effect on DVT:** There was no significant difference in the risk of DVT (RR=1.71, 95% CI: 0.74 to 3.99) (Figure 172, Appendix E).

**Effect on proximal DVT:** There was no significant difference in the risk of proximal DVT (RR=2.00, 95% CI: 0.19 to 21.36) (Figure 174, Appendix E).

## 7.4 Patient views on mechanical vs pharmacological interventions

We found only one study comparing patient views for mechanical interventions with those for pharmacological interventions (Evidence Table 59, Appendix D)[357]. This RCT looked at the views of 207 women undergoing surgery for gynaecological malignancy on low molecular weight heparin or external pneumatic compression devices.

Four per cent of the low molecular weight heparin group reported side effects of discomfort compared to 26% of the external pneumatic compression group who experienced discomfort, inconvenience, problems and/or side effects. The most common side effect associated with the pneumatic compression devices was excessive perspiration. Eleven percent indicated that they removed pneumatic compression device when the nurse was out of the room. The compression device was not optimally functional in 9.6% patients at some point of postoperative recovery period whereas the protocol for low molecular weight heparin was not strictly adhered to in 6.8% patients.

Overall, there was no difference in preference or concordance between external pneumatic compression and low molecular weight heparin even though external pneumatic compression devices appear to lead to more discomfort. However, none of the patients had used the other method of prophylaxis so they had no basis on which to make a comparison.

## 7.5 Economic evidence on mechanical vs pharmacological interventions

### 7.5.1 The studies

We found six studies (Evidence Table 65, Appendix D). The studies evaluated either IPC or GCS. All were decision models. Surgery type was heterogeneous (orthopaedic, general, gynaecological and urological). There was only one UK-based study (the others were mainly from USA plus Canada and South Africa). They mainly estimated health gain in terms of lives saved not QALYs. Most studies included the cost of prophylaxis, diagnosis and treatment of DVT/PE.

However, they did not include long-term prophylaxis or treatment of post-thrombotic syndrome.

### 7.5.2 IPCD vs UFH

Two models found IPCD to be dominant and three found UFH to be dominant. In one more study the cost-effectiveness was indeterminable[253,347,356,410,411,433].

### 7.5.3 Stockings vs UFH

One model found stockings to be dominant and one found UFH to be cost-effective. In one more study the UFH was more effective but cost-effectiveness was indeterminable[410,411,433].

### 7.5.4 IPCD vs Warfarin

One model found IPCD to be dominant[410] and in a cohort study the cost-effectiveness was indeterminable[238].

### 7.5.5 Stockings vs Warfarin

A model found warfarin to be cost-effective[410].

## 7.6 Conclusions

We found no reliable evidence of a difference in the effectiveness between mechanical and pharmacological methods of prophylaxis.

There were no cost-effectiveness studies comparing mechanical devices with low molecular heparin or fondaparinux. Furthermore, for those comparisons where there was economic evidence, there was too much inconsistency in the results. The most important contribution to this heterogeneity is the methods of estimating effectiveness. The trials employed to estimate effectiveness varied and sometimes crude methods of indirect comparison were used to estimate the event rates for each strategy. To ensure that all of the good quality clinical evidence from the guideline is used systematically, we have conducted our own mixed-treatment comparison meta-analysis and cost-effectiveness analysis (Chapters 12 and 13). Recommendations on the most clinically and cost effective mechanical and pharmacological strategies can be found in chapter 13.

# 8 Anaesthesia

## 8.1 Introduction

Anaesthesia is required for most operations and many investigations and other procedures. A general anaesthetic results in a patient losing consciousness. A regional anaesthetic technique involves injecting local anaesthetic into the epidural space (an epidural anaesthetic) or the subarachnoid space (a spinal anaesthetic) to achieve a sensory and/or motor block of the required area. Other drugs such as opioids may be added to the local anaesthetic agents or used as sole agents. Spinal injections are usually given as a single dose with a limited duration of action. Epidural anaesthesia may be continued for hours or days by placing additional medication through a catheter left in the epidural space. Regional techniques may be combined with sedation or a general anaesthetic. Certain procedures such as caesarean section, some urological operations or orthopaedic procedures on the lower limbs, are well suited to the use of regional techniques. Other procedures such as intracranial neurosurgery are not suitable. The use of regional anaesthesia is rare in cardiac surgery but may be used for thoracic and vascular operations.

## 8.2 Clinical evidence on anaesthesia

### 8.2.1 Regional vs General Anaesthesia

We identified one systematic review of 11 RCTs of regional vs general anaesthesia[444] and four additional RCTs giving a total of 15 studies with 1115 participants (Evidence Table 60, Appendix D). Twelve studies were in elective orthopaedic surgery patients, two urological and one in general surgery patients. Eleven studies used an epidural regional anaesthetic and four administered a spinal anaesthetic. Eight of the 11 studies using epidural anaesthesia continued the anaesthetic into the post-operative period for pain relief (in the remaining three studies the duration of the epidural anaesthetic was either unclear or not reported). In seven studies patients were given no prophylaxis for VTE, patients wore stockings in three studies, and received a pharmacological method of prophylaxis in five studies.

Nine studies were conducted in the 1980s and six in the 1990s, with the most recent trial published in 1996. It should be noted that general anaesthetic techniques and other aspects of perioperative management have changed considerably over this period.

**Effect on DVT:** A significant risk reduction for DVT was found in patients receiving regional compared with general anaesthesia (38%) (RR=0.62, 95% CI: 0.53 to 0.73,15 studies) (Figure 175, Appendix E).

**Effect on pulmonary embolism:** Regional anaesthesia was significantly more effective in reducing risk of pulmonary embolism than general anaesthesia, with an overall reduction of 43% (RR=0.57, 95% CI: 0.35 to 0.91) (Figure 176, Appendix E).

**Effect on proximal DVT:** Regional anaesthesia significantly reduced the overall risk proximal deep vein thrombosis compared with general anaesthesia. (RR=0.30, 95% CI: 0.19 to 0.47, seven studies) (Figure 177, Appendix E). The results of one trial[376] contributed 50% of the results.

**Effect on major bleeding:** Seven studies measured major bleeding events. Only one study reported an event, (RR=0.10, 95% CI: 0.01 to 1.71). The difference was not significant (Figure 178, Appendix E).

### 8.2.2 Subgroup Analysis of Epidural vs Spinal Anaesthesia

We found no RCTs comparing spinal and epidural anaesthesia with regard to the development of post-operative VTE. A subgroup analysis of the regional vs general anaesthesia RCTs was carried out to look for a difference in the magnitude of effect based on whether spinal or epidural regional anaesthesia was used. Eleven studies used epidural and four studies used spinal regional anaesthesia.

For deep vein thrombosis, a random effects meta-analysis was used, due to the heterogeneity within the results. Subgroup analyses were not possible for proximal DVT and major bleeding as there were no studies using spinal anaesthesia that assessed these variables.

**Effect on DVT:** A significantly reduced risk of DVT was found with both epidural compared with general anaesthesia (RR=0.62, 95% CI: 0.51 to 0.75, 11 studies) and spinal compared with general anaesthesia (RR=0.63, 95% CI: 0.48 to 0.83, 4 studies). No significant difference in the magnitude of effect between epidural and spinal anaesthesia was found ($\chi^2$ on 1 df = 0.03, p=0.86) (Figure 179, Appendix E).

**Effect on pulmonary embolism:** We found a significantly reduced risk with epidural compared to general anaesthesia (RR=0.61, 95% CI: 0.38 to 0.99, 5 studies). There was no significant difference in risk of developing pulmonary embolism in a comparison of spinal vs general anaesthesia (RR=0.47, 95% CI: 0.23 to 0.96). There was no significant difference in the magnitude of effect between epidural and spinal anaesthesia ($\chi^2$ on 1 df = 0.42, p=0.52) (Figure 180, Appendix E).

### 8.2.3 Regional + general anaesthesia vs general anaesthesia only

One study in the systematic review mentioned above[444] and one further study[124] compared the combined use of regional anaesthesia and general anaesthesia with general anaesthesia alone (Evidence Table 61, Appendix D). One study[124] was in elective hip surgery patients. All patients received an oral anticoagulant for VTE prophylaxis. Patients receiving regional anaesthesia had an epidural for the duration of surgery only. The study was small, with only 37 patients. The second study[235] was of general surgery (elective gall bladder) patients. No VTE prophylaxis was given to patients in the study. For regional anaesthesia patients, the epidural was prolonged into the post-operative period for pain relief. The studies did not report major bleeds or pulmonary embolism. One study[124] reported the site of deep vein thrombosis. No patient had a DVT that was situated above the knee and therefore the relative risk of proximal DVT was not estimable.

**Effect on DVT:** No significant difference was found (RR=0.69, 95% CI: 0.26 to 1.82, two studies) (Figure 181, Appendix E).

### 8.2.4 Risk of haematoma in anticoagulated patients receiving a regional anaesthetic

Risk of haematoma at the injection site is increased with the concomitant use of pharmacological prophylaxis agents. Removal of epidural catheter in the anticoagulated patient has also been associated with the development of spinal haematoma. The consequences of an epidural haematoma may be permanent paralysis below the level of the haematoma. The diagnosis is difficult as patients may have weakness or block because of the effects of the epidural. It would be extremely difficult to determine the true incidence as a randomised study would require very large numbers of patients due to the rarity of the event, however it has been estimated to be about 1 in 150,000 epidural blocks and 1 in 220,000 spinal anaesthetics[82].

## 8.3 Economic evidence on anaesthesia

We did not find any relevant economic evidence in our search of the literature.

## 8.4 Conclusions on clinical and cost effectiveness of anaesthesia

Evidence from RCTs shows that regional anaesthesia compared with general anaesthesia reduces the risk of developing postoperative VTE. There was not enough evidence to determine differences in effect for major bleeding. The evidence is limited to certain surgical procedures and there are other considerations involved when selecting an anaesthetic technique. Patient preferences are also an important consideration.

The GDG considered the evidence that regional anaesthesia reduces the risk of DVT as important. Regional anaesthesia alone should not be considered a suitable method of prophylaxis. There are effective alternative techniques to prevent these complications and other matters to be taken into account when deciding on the most appropriate anaesthetic for a patient. In the absence of data on bleeding and the practical implications for different surgical procedures the group decided to recommend that it's use be considered where practical in addition to other methods of prophylaxis.

An additional concern is the risk of developing a haematoma as a result of a regional anaesthetic technique. Consequently, the GDG recommend that the timing of pharmacological prophylaxis should be carefully planned to minimise the risk of spinal

haematoma if a regional anaesthetic technique is used.

We found no evidence on the cost-effectiveness of regional anaesthesia compared with general anaesthesia in the context of VTE prophylaxis. However, there is a small body of literature that shows regional anaesthesia to be associated with faster recovery time and reduced cost for some types of surgery[372,556]. This would suggest that, when it can be performed safely, regional anaesthesia is likely to be a highly cost-effective form of VTE prophylaxis.

## 8.5 Recommendations

**Regional anaesthesia reduces the risk of venous thromboembolism compared with general anaesthesia. Its suitability for an individual patient and procedure should be considered, along with the patient's preferences, in addition to any other planned method of thromboprophylaxis.**

**If a regional anaesthetic technique is used, the timing of pharmacological prophylaxis should be carefully planned to minimise the risk of haematoma.**

# 9 Nursing care, physiotherapy and hydration to reduce the risk of VTE

## 9.1 Early mobilisation and leg exercises

Immobility and lack of exercise are widely accepted as risk factors for developing venous thromboembolism. When normal venous pump function is lost as a result of bed rest, venous stasis manifests itself in two ways. Firstly, there is a decrease in the linear velocity of blood, affecting venous return from the lower extremities. Secondly, this decrease in the mean flow and pulsavity of the venous flow is followed by dilatation of the vein delaying further venous return and leading to venous stasis.

It has long been suggested that early mobilisation prevents stasis and reduces subsequent risk of thrombi formation[291,551]. Although there is no robust clinical data or RCTs, attesting to support the value of early mobilisation in combating venous stasis, experimental physiology has demonstrated that it promotes venous return and thus reduces the risk of VTE[187,484].

Leg exercises are a safe and effective method of increasing venous return to the heart. The contraction during leg exercises, particularly the calf muscle pump, compresses the deep leg veins and with the aid of the venous valves, moves blood flow toward the heart. Mechanical devices that perform continuous passive motion imitate these contractions and increase the volume and velocity of venous flow.

### 9.1.1 Clinical evidence on early mobilisation and leg exercises

We identified no RCTs that looked at the effect of early mobilisation or leg exercises on venous thromboembolism outcomes measured using objective criteria.

### 9.1.2 Economic evidence on early mobilisation and leg exercises

We did not find any relevant economic evidence.

### 9.1.3 Conclusions on early mobilisation and leg exercises

There is no RCT evidence to contradict the practices of encouraging patients to mobilise early or exercising their legs while immobile in bed.

The GDG recommended that it is good practice to encourage patients to mobilise as soon as possible after surgery and that leg exercises should be encouraged in immobilised patients.

## 9.2 Leg elevation

Leg elevation has a dual physiological effect: it reduces limb swelling and promotes venous return by its gravitational effect. It is generally held that promoting venous return can contribute to the prevention of thrombi formation. n addition, postural changes in the supine position can have a haemodynamic effect and are associated with an increase in blood flow in deep veins and reduction in venous pressure.

### 9.2.1 Clinical evidence on leg elevation

We found one RCT[447] that compared foot elevation with no intervention (Evidence Table 62, Appendix D). Twenty five mixed surgical patients (elective surgery excluding surgeries performed on the leg below groin) were randomised to either bilateral leg elevation at 15 degrees from pre-medication until one week post surgery, or no leg elevation. The study did not report whether patients received any other VTE prophylaxis. Pulmonary embolism and major bleeding events were not reported.

**Effect on DVT:** No significant difference was found between leg elevation and no leg elevation (RR=1.08, 95% CI 0.35 to 3.40, one study) (Figure 182, Appendix E).

**Effect on proximal DVT:** Due to the low event rates and small size of the trial, it was not possible to obtain a reliable estimate of the effect on

proximal DVT (RR=1.08, 95% CI 0.08 – 15.46, one study) (Figure 183, Appendix E).

### 9.2.2 Economic evidence on leg elevation

We did not find any relevant economic evidence.

### 9.2.3 Conclusions on leg elevation

Overall, there is little scientific data and further robust studies are warranted to reliably assert that leg elevation is effective in reducing the risk of VTE. Caution must be used with leg elevation in patients with ischaemic legs.

## 9.3 Continuous passive motion

Continuous passive motion (CPM) is where a joint is moved continuously, either by another person bending it or by a machine. The CPM machine produces continuous passive motion by slowly and gently bending and straightening the knee without the assistance of the individual. CPM applied to the ankle joint may increase the volume of flow in the femoral vein within minutes and much higher after several minutes. These positive effects are evident even after the device is turned off[177].

### 9.3.1 Clinical evidence on continuous passive motion

We identified no RCTs of continuous passive motion that looked at the effect of this intervention on VTE outcomes measured using objective criteria.

### 9.3.2 Economic evidence on continuous passive motion

Two cost analyses compared continuous passive motion with conventional physiotherapy after total knee replacement. There was one RCT[361], and one non-RCT[540], both set in the USA. The RCT was not included in the clinical evidence above because it did not state how DVTs were diagnosed. This is probably because VTE was not a primary outcome of the study. However, this was not considered a good reason to exclude the cost analysis.

Both studies found cost savings of about £120 per patient due to the avoidance of physical manipulation in some patients but these differences were not statistically significant. The RCT reported one DVT in the CPM arm but neither study systematically screened patients for DVT. Hence the cost-effectiveness of CPM is uncertain.

### 9.3.3 Conclusions on continuous passive motion

There is little evidence on continuous passive motion. Further investigation is necessary before continuous passive motion can be reliably recommended.

## 9.4 Hydration

It is believed that dehydration predisposes to venous thromboembolism. Kelly et al found a strong association between dehydration after acute ischaemic stroke and VTE[288]. Allowing a patient to become dehydrated during surgery may also be associated with VTE.

### 9.4.1 Clinical evidence on hydration

We found one RCT[265] that looked at the effect of intravenous saline administration on post-operative deep vein thrombosis(Evidence Table 63, Appendix D). Sixty patients undergoing routine abdominal surgery were randomised. Thirty patients received 1 litre of Hartmann's solution per hour of surgery, and then 2-3 litres of dextrose-saline per 24 hours for 2 days. Patients in the second group were given no intravenous fluids either during or after the surgery, but small, increasing amounts of water were allowed by mouth from the first day onwards. The study did not report location of thrombosis, pulmonary embolism or major bleeding events.

**Effect on DVT:** Intravenous saline was associated with a significantly higher number of DVT events (RR=4.50, 95% CI 1.06-19.11, one study) (Figure 184, Appendix E).

### 9.4.2 Economic evidence on hydration

We did not find any relevant economic evidence.

### 9.4.3 Conclusions on hydration

We found no RCTs that looked at the effect of oral hydration on venous thromboembolism. The guideline development group considered that it was good practice to recommend that patients having surgery should not be allowed to become dehydrated during their stay in hospital.

## 9.5 Patient views on this group of interventions

No studies on patient views were identified.

## 9.6 Conclusions on clinical and cost-effectiveness of nursing care, physiotherapy and hydration

There is very little evidence on these interventions and where available, the evidence was inconclusive. The GDG made a number of good practice points on hydration, early mobilisation and leg exercises (see below).

## 9.7 Recommendations

**Healthcare professionals should not allow patients having surgery to become dehydrated during their stay in hospital.**

**Healthcare professionals should encourage patients to mobilise as soon as possible after surgery.**

**Healthcare professionals should arrange for immobilised patients to have leg exercises.**

.

# 10 Vena caval filters

## 10.1 Introduction

Vena caval filters are placed in the inferior vena cava by radiologically controlled percutaneous techniques. Their purpose is to trap the thrombus which comes free from the veins of the lower limbs or pelvis and to prevent them reaching the pulmonary circulation. In the earlier designs, once placed they could not be removed, but retrievable and temporary filters are now available. They are usually used in patients who have a known DVT and who may have already had an embolism or for patients in whom anticoagulation is contraindicated.

Filter placement necessitates instrumentation of the veins, either via the groin (Femoral vein) or the neck (jugular vein) and there are complications associated with placement. These can occur immediately following placement or develop or come to light months to years later[213]. The complications include misplacement, pneumothorax, haematoma, air embolism, inadvertent carotid artery puncture and arteriovenous fistula.

## 10.2 Clinical evidence on vena caval filters

We found no RCTs investigating vena caval filters, either permanent or retrievable, in surgical patients.

We identified one RCT that compared the use of permanent vena caval filters with no filters in 400 hospitalised patients with proximal DVT considered to be at high risk of pulmonary embolism[131] (Evidence Table 64, Appendix D). All patients received oral anticoagulants from the 4th day of the study and continued for at least 3 months. Patients were also randomised to receive either UFH or LMWH for 8 to 12 days.

Significantly more patients had a pulmonary embolism in the first 12 days in patients without the filter than in those with the filter. More patients in the group allocated no filters had symptomatic pulmonary embolism than those allocated filters at 2 years and 8 years. The difference was significant at 8 years[515]. There was no difference in the number of major bleeds. However, significantly more patients using filters had recurrent DVT at 2 years.

## 10.3 Economic evidence on vena caval filters

We found no economic studies evaluating vena caval filters specifically in surgical patients. However, we did find five economic studies that evaluated vena caval filters in other contexts (Evidence Table 65).

Two decision models [77,97] compared the surgical placement of vena caval filters with anticoagulation in high-risk trauma patients and in patients with malignant brain tumour. Both studies found that the filter was not cost-effective. A third decision model[468] found that vena caval filter placement is cost-saving compared with either anticoagulation or observation for patients with advanced cancer. However, their assumption of a 90% reduction in symptomatic VTE attributable to filters seems optimistic compared with the RCT results above.

Four studies, three cohort studies[77] and one decision model[60,140,263] found that bedside percutaneous placement of vena caval filters was less costly and safe compared with surgical placement.

## 10.4 Conclusions on clinical and cost effectiveness of vena caval filters

We found no evidence on the effectiveness of vena caval filters in surgical patients. We did find evidence that vena caval filters are effective at reducing the risk of PE in hospitalised patients, although these patients did receive anticoagulation at day 4 of the study. The economic data showed that vena caval filters are unlikely to be cost-effective in patients that can be coagulated.

The British Committee for Standards in Haematology have produced guidelines on the use of vena caval filters[80]. They reviewed the clinical studies mentioned above and came to a consensus on the recommendations.

Given the evidence (extrapolated form non-surgical populations) and the consensus from the previous guideline, the GDG recommend that vena caval

filters should be considered for surgical patients with recent (within one month) or existing venous thromboembolism, but only for patients in whom anticoagulation is contraindicated.

## 10.5 Recommendations

**Vena caval filters should be considered for surgical inpatients with recent (within 1 month) or existing VTE and in whom anticoagulation is contraindicated.**

# 11 Patient Information

## 11.1 Introduction

The aim of this section was to examine whether educating patients about venous thromboembolism before or after surgery reduced the number of postoperative DVTs and pulmonary embolisms or affected any of the other outcomes listed in section 3.4.

We searched for any study, regardless of study design, that examined the effect of giving information on venous thromboembolism or on methods of prophylaxis to patients before or after surgery.

## 11.2 Summary of identified studies

We found no studies that addressed this question.

## 11.3 Conclusions on Information for Patients

Although we did not identify any studies on this, the guideline development group considered that it was good practice to offer patients prior to surgery verbal and written information on the risks of VTE that should include information on the effectiveness of prophylaxis in order to encourage concordance.

There was no evidence on giving patients information on VTE at their discharge from hospital after surgery. However, the guideline development group considered that it was good practice to give patients information on the signs and symptoms of VTE, information on how to use any prophylaxis that they will be administering at home and, in order to strengthen the message, the implication of not using these methods correctly.

## 11.4 Recommendations

**Healthcare professionals should give patients verbal and written information, before surgery, about the risks of VTE and the effectiveness of prophylaxis.**

**Healthcare professionals should give patients verbal and written information on the following, as part of their discharge plan:**

- **The signs and symptoms of DVT and PE.**
- **The correct use of prophylaxis at home.**
- **The implications of not using the prophylaxis correctly.**

# 12 Mixed Treatment Comparisons Meta-analysis

## 12.1 Rationale

It is difficult to decide which prophylaxis strategy is the most-effective at reducing VTE just from looking at the results of conventional meta-analyses of direct evidence (as presented in chapters 5-10) for two reasons:

1. Some pairs of alternative strategies have not been directly compared in an RCT (For example, danaparoid vs fondaparinux).

2. There are frequently multiple overlapping comparisons (For example, heparin vs no prophylaxis, heparin vs stockings and stockings vs no prophylaxis), that could potentially give inconsistent estimates of effect.

To overcome these problems, we conducted a mixed treatment comparisons (MTC) meta-analysis that pools together all the data. This allowed us to rank the different prophylaxis interventions in order of efficacy at reducing the number of DVTs and in order of risk of major bleeding. It also gives us a single estimate of effect (with confidence intervals) for each intervention. These estimates are essential to facilitate a cost-effectiveness analysis of various prophylaxis strategies.

The MTC analyses are used to compliment our analysis of direct comparison evidence. The particular approach to MTC analysis we have taken allows us to estimate the level of inconsistency between different comparisons.

The MTC analysis gives us greater statistical power in evaluating combination prophylaxis an area where the trial evidence was limited. For example we can get more precise estimates of the effectiveness of LMWH+mechanical by utilising both trials of LMWH adjuvant to mechanical and trials of mechanical adjuvant to LMWH.

## 12.2 Interventions

The thromboprophylaxis interventions compared in the model are those we found in the RCTs included in our clinical review (chapters 5-10). However, to simplify the task, we have excluded trials that evaluated:

- dextran, antiplatelet drugs other than aspirin, fixed-dose oral anticoagulants – since these are unlicensed, dated, and not likely to be recommended

- different anaesthetic regimes, since for most of our studies patients had a mixture of types of anaesthesia

- hydration, physiotherapy, continuous passive motion, foot elevation, electrical stimulation and vena caval filters, where there was insufficient RCT evidence.

- combinations of two or more drugs and combinations of two or more mechanical devices, where there was insufficient RCT evidence

- post-discharge prophylaxis

For trials of three or more arms, we excluded only the arm that is outside of this inclusion criterion, not the whole trial.

Interventions that we *included* are:

### Pharmacological:

- aspirin, danaparoid, fondaparinux, heparin (UFH / LMWH), adjustable-dose oral anticoagulants (OAC-adj)

### Mechanical:

- stockings, intermittent pneumatic compression device (IPCD), foot impulse devices

- nil (i.e. no prophylaxis or placebo)

- combinations of one drug and one mechanical device

- combinations of two mechanical devices (as a sensitivity analysis).

In some studies, the majority but not all patients were using mechanical prophylaxis in the background of the trial. This was the case for the

fondaparinux vs LMWH trial. For the base case analysis we ignored background prophylaxis. But as a sensitivity analysis, we reclassify these studies as Mech+Fondaparinux vs Mech+LMWH.

## 12.3 Methods

To estimate the relative risks we performed a maximum likelihood mixed-treatment comparison meta-analysis that simultaneously uses all the RCT evidence[342] – for details see appendix F. As with conventional meta-analyses, this analysis does not break the randomisation of the evidence. Nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular prophylaxis combination is derived only from RCTs that had that particular combination in a trial arm.

Data from all the relevant RCTs in our clinical review (Chapters 5, 6 and 7) were included in the analysis.

We produced five MTC models:

- **DVT MTC analysis 1** *Single intervention*. We took into account single prophylaxis interventions only and explicitly excluded combined strategies.

- **DVT MTC analysis 2** *Single/combined DVT meta-analysis*. We combined all the mechanical devices into one category (Mech). We also added in two combination strategies Mech+UFH and Mech+LMWH.

- **DVT MTC analysis 3** *Same as Analysis 2) but adding a strategy of two mechanical devices: 'Double Mech'*.

- **DVT MTC analysis 4** *Same as Analysis 2) except that studies that were categorised as Fondaparinux vs LMWH are reclassified as Mech+Fondaparinux vs Mech+LMWH,* since most patients in all of these studies were reported to be using a background mechanical prophylaxis.

- **Major bleeding MTC analysis.** Mechanical devices do not influence major bleeding so for this model mechanical only strategies were re-categorised as "Nil". Likewise combination strategies were categorised according to their drug component only.

## 12.4 Results

The *single intervention meta-analysis* was composed of 220 studies including 55,037 patients. Of these patients, 8048 experienced DVT. The *single/ combined meta-analysis* was composed of 240 studies including 58,645 patients. Of these 8,814 experienced DVT. The *combined + two mechanical devices meta-analysis* was composed of 248 studies including 58,887 patients. Of these, 8908 experienced DVT. The *major bleeding meta-analysis* was composed of 123 studies including 56,621 patients, of whom 1769 had a major bleeding event.

For each strategy, the results are given in terms of the relative risk (RR) compared to the nil prophylaxis strategy. We took the nil prophylaxis strategy data from both placebo and open no-prophylaxis trial arms.

The results for the *single intervention meta-analysis* (see Diagram 1) show that fondaparinux performs best overall with a 78% relative risk reduction (RR=0.22, 95% CI: 0.16 to 0.28) compared to no prophylaxis. The mechanical treatments (intermittent pneumatic compression IPCD, foot pumps FP and graduated compression stockings GCS) show a similar relative risk (0.46, 0.53 and 0.53 respectively) with overlapping confidence intervals.

**Diagram 1**: DVT MTC analysis 1: single intervention strategies

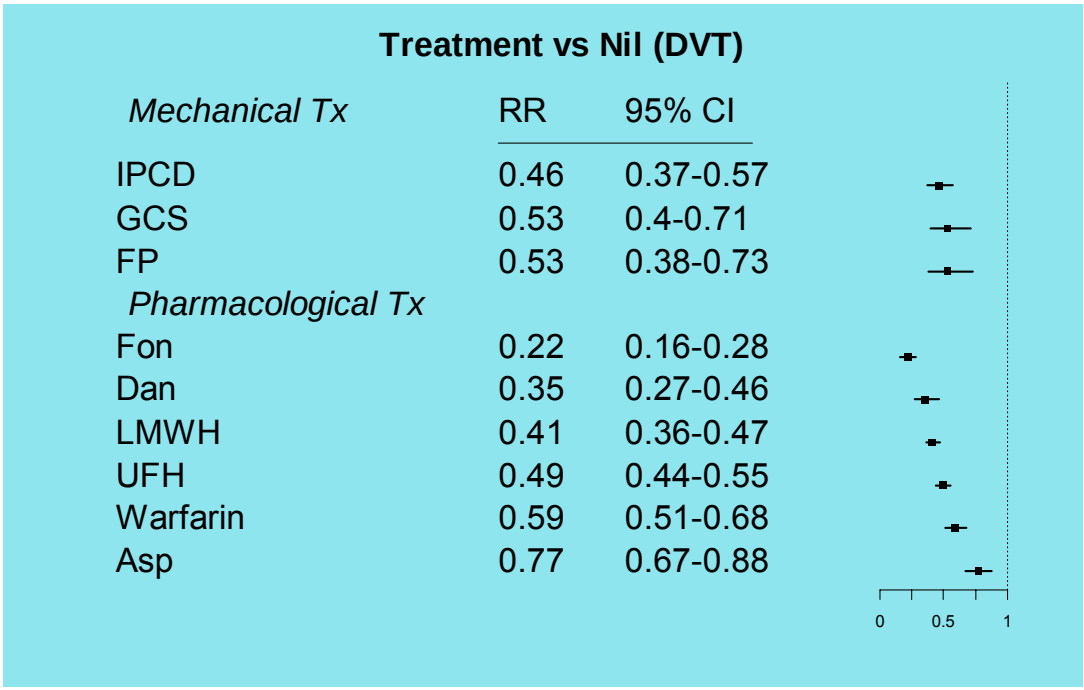



Diagram 2 shows the results of the *combined methods analysis*, that is, when the mechanical methods are combined and treated as one group. The results are very similar to the *single intervention DVT meta-analysis*. This strategy shows a relative risk reduction of 51% (RR=0.49, 95% CI: 0.43 to 0.57).

The combined strategies (LMWH+Mech and UFH+Mech) perform better than mechanical and most of the pharmacological treatments alone with a relative risk reduction of 71% and 70% respectively (RR=0.29, 95% CI: 0.22 to 0.37 and RR=0.30, 95% CI: 0.23 to 0.40). Fondaparinux is the only single strategy that is more effective at reducing DVTs.

**Diagram 2**: DVT MTC analysis 2: a) Mechanicals combined b) Combinations added

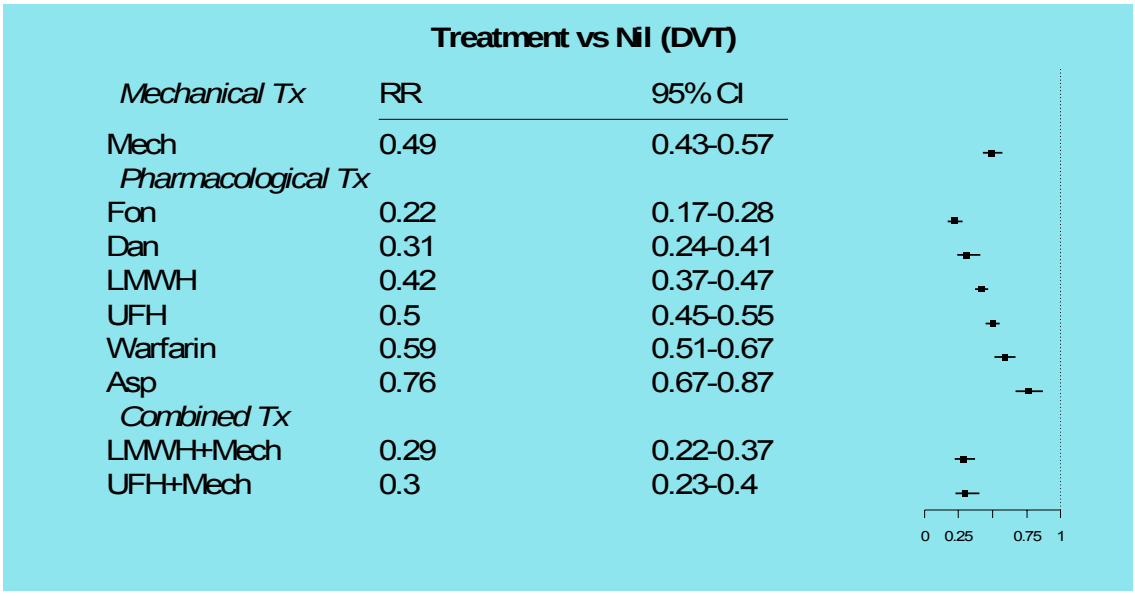



Diagram 3 shows the results of the combined methods analysis but with the strategy of two mechanical devices added into the analysis giving a relative risk reduction of 75% (RR=0.25, 95% CI: 0.16 to 0.38). Two mechanical devices perform better overall, while the other options show very similar results to the previous meta-analysis. However, this data comes from a few small trials

and the GDG did not consider this evidence to be robust.

**Diagram 3**: DVT MTC analysis 3: double mechanical added

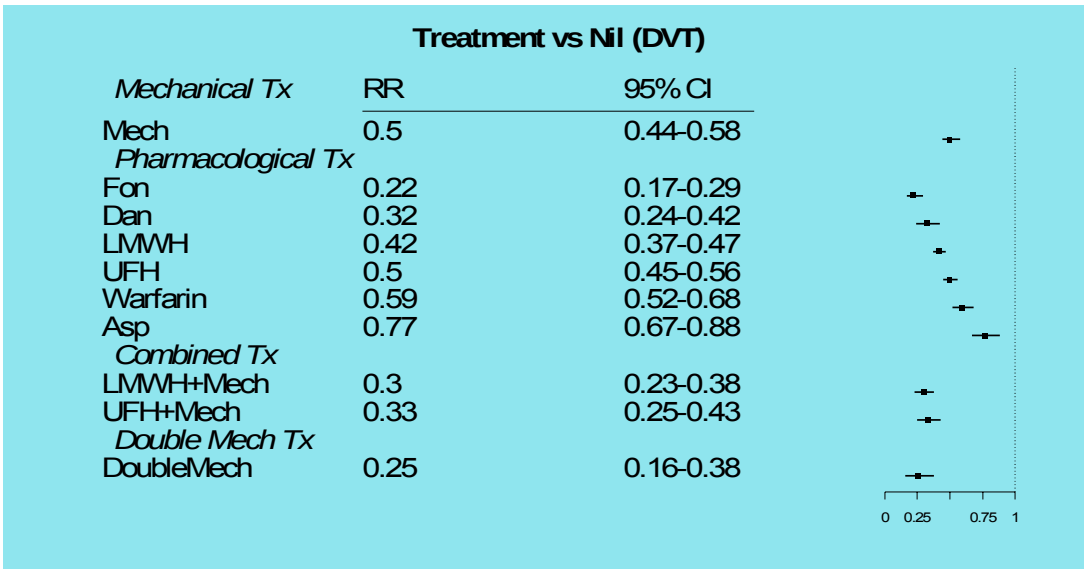
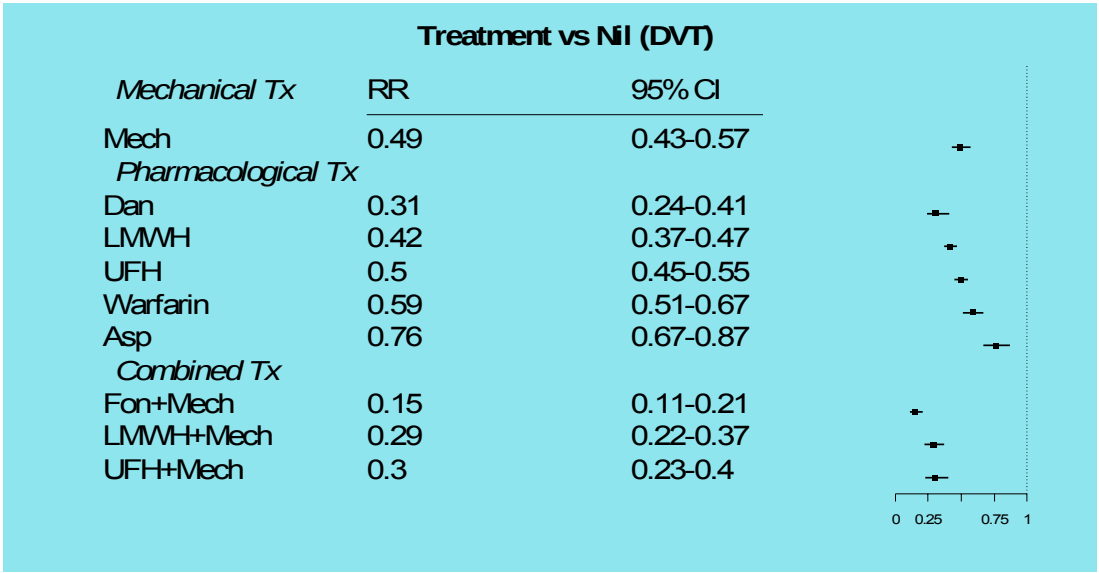


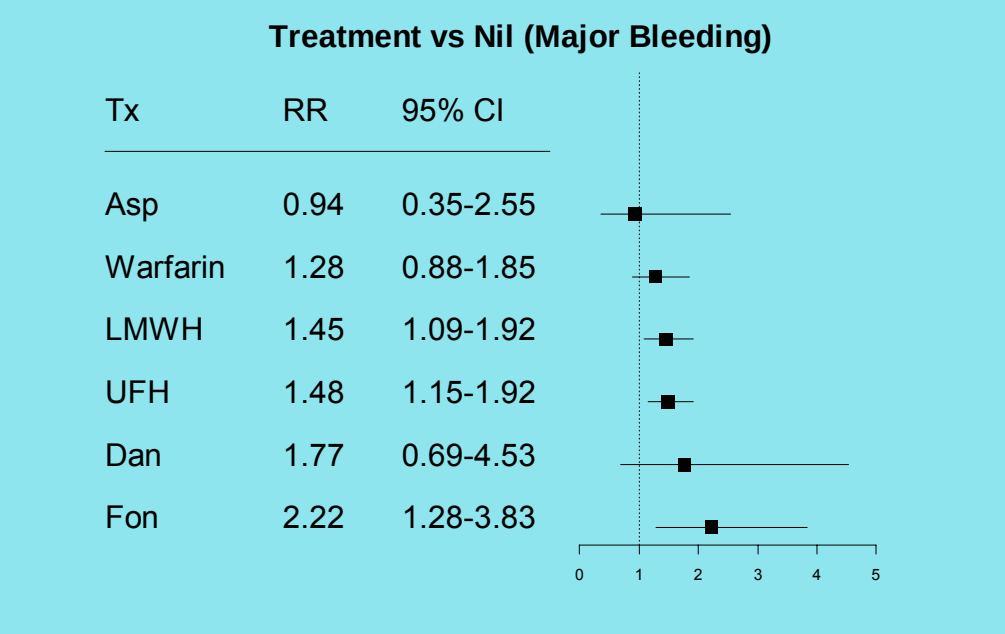

Diagram 4 shows the results of the combined methods analysis except that studies that were categorised as Fondaparinux vs LMWH are reclassified as Mech+Fondaparinux vs Mech+LMWH This gave a relative risk reduction of 85% (RR=0.15, 95% CI: 0.11 to 0.21) for Mech+Fondaparinux.

Diagram 4**: DVT MTC analysis 4: Fondaparinux+Mech added**




Results for the *major bleeding meta-analysis* are shown below. There appears to be a trade-off between effectiveness in reducing the risk of DVT and increased major bleeding. Fondaparinux, which was the most effective pharmacological treatment in reducing the risk of DVT, had the highest estimated relative risk increase for major bleeding, with a relative risk increase of 122% (RR=2.22, 95% CI: 1.28 to 3.83). However the broad confidence intervals for all the strategies overlap, making it difficult to distinguish the different options in terms of major bleeding.

**Diagram 5**: Major bleeding MTC analysis




## 12.5 Discussion

This analysis allowed us to combine the findings from many of the different comparisons presented in the previous chapters. Using this approach we have been able to make comparisons between different prophylactic strategies even when direct comparative data did not exist or the results gave inconsistent estimates of effectiveness.

The ordering of interventions observed in these MTC analyses seems consistent with the results of our review of direct comparison evidence.

However, the analysis performed has some limitations:

- Firstly, there are some important treatment options, such as warfarin combined with mechanical, that have not been addressed in the meta-analysis because of insufficient data.
- Some important outcomes such as mortality and pulmonary embolism have not been examined in the meta-analysis. It difficult to analyse these outcomes with a mixed treatment comparison approach because these events are rare. And we didn't have access to additional information such as time to event which would have made more sophisticated analysis possible.
- There was heterogeneity in the methods and results of the included studies (including differences in the dose, timing and duration of interventions, in addition to differences in study populations). We used a random-effects model, which estimates wider confidence intervals to account for heterogeneity. However, we have not sought to formally identify specific determinants of the heterogeneity observed in the results.

The observed trade-off between DVT and major bleeding implies that a cost-effectiveness analysis, which explicitly evaluates the net impact of DVT, major bleeding and opportunity cost, is essential.

# 13 Cost-effectiveness analysis

We found a number of economic evaluations in the published literature (Chapters 5-7) but still it was necessary to develop our own analysis to determine the most cost-effective thromboprophylaxis strategy for different surgical scenarios. We took this approach because we found great inconsistency in the published economic evaluations mainly because they varied in the clinical studies they included and because they used crude methods to deal with indirect comparisons. Furthermore most of the published studies did not evaluate cost-effectiveness using NICE's reference case.

## 13.1 Methods

We took a 4-stage approach:

1. Compare the different drug interventions

3. Evaluate mechanical prophylaxis

4. Evaluate the addition of a drug as an adjunct to mechanical prophylaxis.

5. Evaluate drug prophylaxis in the post-discharge period in high risk groups.

The thromboprophylaxis interventions we compared in the model are those which we evaluated in our mixed-treatment comparisons meta-analysis (Chapter 12). A combinations of two types of mechanical prophylaxis was not included in the base case analysis because the data are from only a few small trials and the GDG did not consider this evidence to be robust.

The primary outcomes (relative to 'no prophylaxis') are quality-adjusted life-years (QALYs) gained and incremental cost.

### 13.1.1 General methodology

- The effects were derived from the mixed treatment comparisons meta-analysis reported in Chapter 12.

- We performed a probabilistic sensitivity analysis to test the robustness of the results to the imprecision of these estimates and the other model parameters.

- The model employed a cost-effectiveness threshold of £20,000 per QALY gained, complying with the reference case advocated by NICE[389], such that costs were estimated from an NHS and personal social services perspective and both future costs and QALYs were discounted at 3.5%.

A detailed description of our methods can be found in Appendix G.

### 13.1.2 Key assumptions

a) We made the assumption that the *relative* risk (RR) change of each prophylaxis strategy is constant regardless of type of surgery and therefore we pooled together the results of RCTs from all surgical categories.

b) Not every study collected PE data and given the rarity of the event, relative risks are imprecise, so we assumed that the RR reduction in symptomatic PE (Fatal and other symptomatic) is exactly the same as for DVT.

c) Similarly we assumed that the RR increase in fatal bleeds and strokes would be exactly the same as for major bleeding overall.

d) For our main analysis, we assumed prophylaxis does not reduce the incidence of PTS or VTE recurrence.

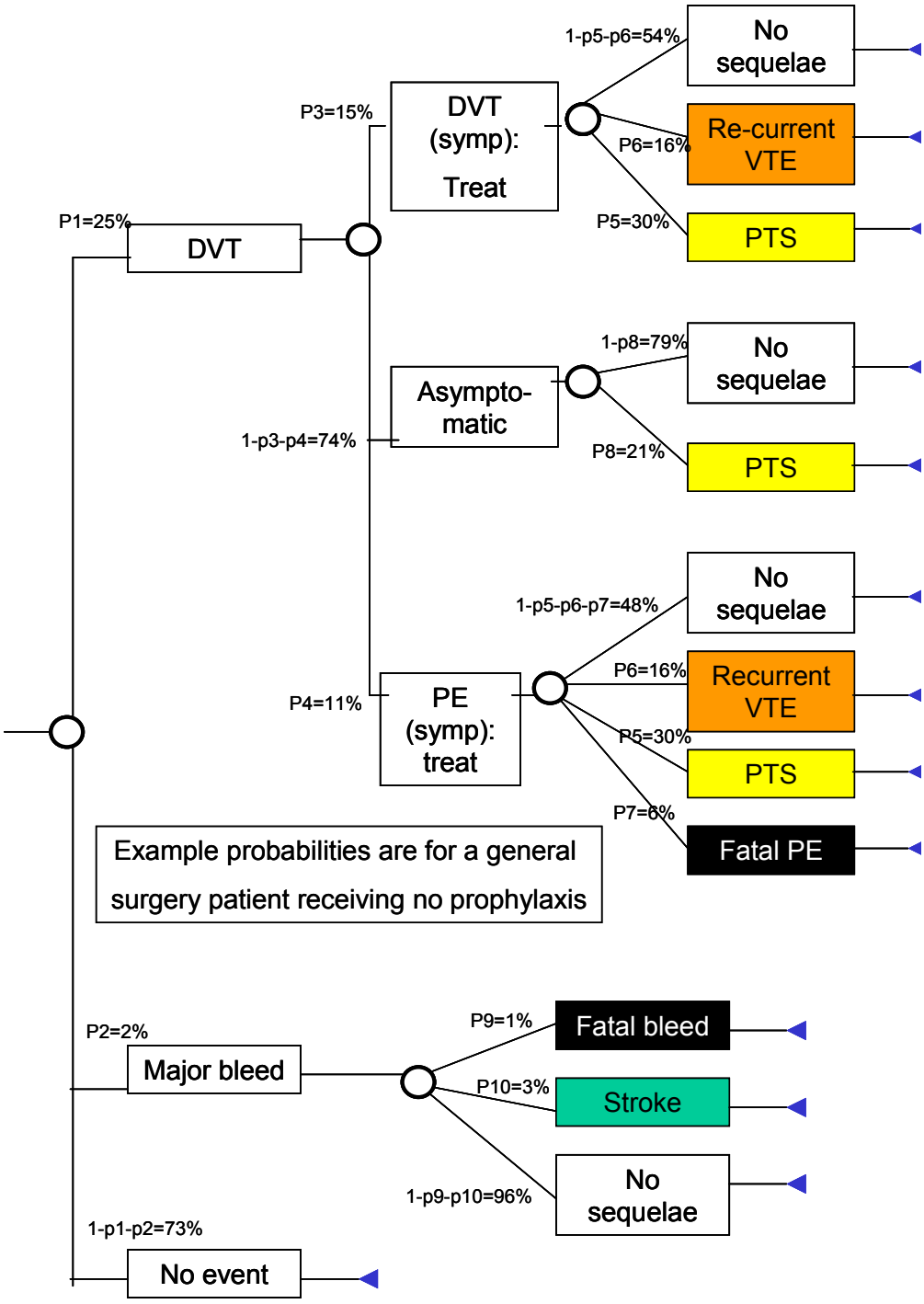
e) For our analysis of in-hospital prophylaxis we assume that prophylaxis is continued until discharge, as was the practice in most of the the RCTs in our review

f) Drug costs were calculated on the basis of the public list price.

g) We conducted a separate analysis of post-discharge prophylaxis. The model structure is the same as the for in-hospital prophylaxis. The only differences are in terms of 1) the baseline risk (based on the risk in the control arms of *post-discharge* RCTs, 2) the relative risks (based on the post-discharge RCTs), 3) the interventions compared (only LMWH, fondaparinux and no prophylaxis are considered post-discharge).

A diagrammatic representation of the model can be found in Diagram 6.

**Table 6: Decision model**




Notes: Figures are rounded to the nearest %

- In the base case model only the following probabilities are modified according to the prophylaxis strategy: p1 and p2
- In the base case model the costs and health consequences of PTS and recurrence are not included.
- The diagram represents only the incidence of events and not the sequence. E.g. a patient who is scanned in hospital might show no DVT but could still develop a symptomatic VTE post-discharge.

### 13.1.3 Surgical scenarios

We constructed a cost-effectiveness analysis for each of four common types of surgery:

- hip fracture
- elective hip
- gynaecological surgery (hysterectomy)
- general surgery.

Table 7 summarises all of the differences between types of surgery that were captured by the model. Age, sex and standardised mortality ratio contribute to the estimates of life expectancy and subsequently the magnitude of QALYs gained from averting a fatal PE and the magnitude of QALYs lost from incurring a fatal bleeding event. Length of stay impacts on the cost of prophylaxis. The baseline risk of events affects the magnitude of treatment costs (or savings) and the magnitude of QALYs gained (or lost).

**Table 7: Surgical scenarios – summary of differences**

| | Source | Hip Fracture | Elective Hip | Gynaecological (hysterectomy) | General surgery |
|---|---|---|---|---|---|
| **HES code** | HES 2004-5[134] | W46, W47, W48 | W37, W38 | Q07.4 | Various |
| **Mean age (years)** | HES 2004-5[134] | 82 | 70 | 50 | 60* |
| **% Male** | HES 2004-5[134] | 21% | 38% | 0% | 50%* |
| **Standardised Mortality Ratio**** | Epidemiological cohort study[480] (1st year after surgery) | 461% (432, 491) | 83% (71, 97) | 77% (50, 114) | 100%** |
| **Mean LOS / duration of prophylaxis** | HES 2004-5[134] (days) | 20 | 10 | 6 | 7* |
| **PE fatality rate***** | See Appendix G Table 4 | 31% | 6% | | |
| **Baseline risk in the absence of prophylaxis (during hospital admission)** | | | | | |
| **DVT risk** | See Chapter 4, Table 2 | 39% | 45% | 16% | 25% |
| **Symptomatic PE risk** | See Chapter 4, Table 2 | 6% | 4% | 1% | 2% |
| **Major bleeding risk** | See Chapter 4, Table 3 | 3% | 2% | 4% | 2% |
| **Baseline risk post-discharge in the absence of post-discharge prophylaxis** | | | | | |
| **DVT risk** | See Appendix G, section 3 | 19% | 21% | 8% | 13% |
| **Symptomatic PE risk** | See Appendix G, section 3 | 1.5% | 1% | 0.25% | 0.5% |
| **Major bleeding risk** | See Appendix G, section 3 | 0.1% | 0.1% | 0.1% | 0.1% |

* Based on the average patient characteristics of the general surgery RCTs in our clinical review, ** Assumed, *** Fatal PEs divided by all symptomatic PEs, **** Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex.

### 13.1.4 Data sources

The estimates of relative risk for the in-hospital prophylaxis strategies are presented in Chapter 12. For extended prophylaxis the data was more limited and therefore we simply used the relative risks compared with no post-discharge prophylaxis from our direct comparison meta-analyses (Chapter 6). Baseline risk data was estimated from the RCT

Table 8). Members of the GDG devised typical treatment pathways and these were costed using unit costs from standard NHS sources. Drugs were costed using the BNF list price. The QALYs lost associated with a fatal event would vary according to the patient group. We estimated average life-

data where there was a no prophylaxis arm (Chapter 4). Other probabilities were taken from the published literature and were from systematic reviews when available.

In addition to the cost of prophylaxis, we included the treatment costs associated with symptomatic VTE and bleeding events (

years for each surgical scenario using life tables for England & Wales based on the groups age-sex structure and modified using published standardised mortality ratios. We took quality of life weightings from the published literature. The QALY weightings for the general surgery patient are shown in

Table 8 – details are in Appendix G.

**Table 8: Summary of the consequences of each event**

| Events | Additional treatment cost | QALYs lost (General surgery patient) |
|---|---|---|
| | | |
| Fatal PE | £0 | 7.730 |
| Fatal bleed | £0 | 7.730 |
| Symptomatic DVT | £476 | 0.004 |
| Symptomatic PE (non-fatal) | £2,498 | 0.017 |
| Asymptomatic DVT | £0 | 0 |
| Asymptomatic PE | £0 | 0 |
| Major bleed (stroke) | £7,744 | 0.320 |
| Major bleed (other non-fatal) | £1,160 | 0.011 |

In the next section, we present results both in tables and graphs.

The tables report incremental net benefit (INB). The formula for INB is:

*INB= (QALYs gained x £20,000) minus the incremental cost*

This indicates that we will invest up to £20,000 to gain one additional QALY. The strategy that has the highest INB is the optimal (that is, most cost-effective) strategy. Strategies that have a negative INB are not cost-effective even compared with no prophylaxis.

The graphs show incremental cost plotted against QALYs gained for each strategy (compared with nil); this is known as the cost-effectiveness plane. Strategies that appear in the bottom right quadrant are cost saving as well as health improving compared with no prophylaxis. A strategy that is 'dominant' will be both lower than and to the right of every other strategy. Strategies that occur in the top left or bottom left quadrants are damaging to health (because the benefits from averting VTEs are more than offset by the health loss from increased major bleeding).

## 13.2 In-hospital prophylaxis: the general surgery patient

The details for these patients are given in Table 7. They have a high risk of DVT and symptomatic pulmonary embolism but not as high as for patients undergoing major orthopaedic surgery.

### 13.2.1 Drug prophylaxis

Using our best estimates for all of the model parameters, we found that fondaparinux was the most cost-effective drug strategy (Table 9 and Table 10). Diagram 6 shows the extent of our uncertainty due to the standard error around our estimates of relative risk (keeping all other parameters constant). The confidence ellipses are very slim – this is because there is strong negative correlation between costs and effects (the more VTEs we avert the more we increase health gain *and* the more we increase cost savings). Randomly varying all of the model parameters simultaneously, we found that fondaparinux was optimal for 45% of simulations, followed by LMWH in 36%.

**Table 9: Events by type of in-hospital single drug prophylaxis - general surgery patient**

| | All DVT | Sympto-matic DVT | Fatal PE | Sympto-matic PE non-fatal | | All Major bleed | Fatal Bleed | Stroke |
|---|---|---|---|---|---|---|---|---|
| Nil | 24.9% | 3.8% | 0.16% | 2.5% | | 2.1% | 0.02% | 0.07% |
| Aspirin | 19.1% | 2.9% | 0.12% | 1.9% | | 2.0% | 0.02% | 0.07% |
| Danaparoid | 8.8% | 1.3% | 0.06% | 0.9% | | 3.7% | 0.04% | 0.13% |
| Fondaparinux | 5.4% | 0.8% | 0.03% | 0.5% | | 4.7% | 0.05% | 0.16% |
| LMWH | 10.3% | 1.6% | 0.06% | 1.0% | | 3.0% | 0.03% | 0.10% |
| OAC-adj | 14.6% | 2.2% | 0.09% | 1.4% | | 2.7% | 0.03% | 0.09% |
| UFH | 12.3% | 1.9% | 0.08% | 1.2% | | 3.1% | 0.03% | 0.11% |

* FID=Foot impulse device, GCS=graduated compression stockings, IPCD=intermittent pneumatic compression devices, OAC-adj=adjustable-dose oral anticoagulants, LMWH=low molecular weigh heparin, UFH=unfractionated heparin

**Table 10: Cost-effectiveness of drug-only prophylaxis – general surgery patient**

| Strategy | QALYs gained per patient compared with Nil | Incremental cost per patient compared with Nil | Incremental net benefit per patient compared with Nil |
|---|---|---|---|
| Nil | - | £0 | £0 |
| Aspirin | 0.0031 | -£13 | £74 |
| Danaparoid | 0.0065 | £400 | -£269 |
| Fondaparinux | 0.0073 | £25 | £121 |
| LMWH | 0.0064 | £11 | £117 |
| OAC-adj* | 0.0046 | £26 | £66 |
| UFH | 0.0053 | £18 | £89 |

### 13.2.2 Mechanical prophylaxis

Mechanical prophylaxis dominates no prophylaxis and Table 12).

### 13.2.3 Combination prophylaxis (Table 11 and Table 12)

Adding LMWH or fondaparinux to mechanical prophylaxis is not cost-effective (£25,000 or £34,000 per QALY gained). Therefore the optimal strategy is mechanical prophylaxis.

Diagram 8 shows the extent of our uncertainty due to the standard error around our estimates of relative risk (keeping all other parameters constant). Randomly varying *all* of the model parameters simultaneously, we found that mechanical was optimal for 61% of simulations and combination prophylaxis was optimal for 39%.

**Table 11: Events with combination prophylaxis - general surgery patient**

| | All DVT | Sympto-matic DVT | Fatal PE | Sympto-matic PE non-fatal | | All Major bleed | Fatal Bleed | Stroke |
|---|---|---|---|---|---|---|---|---|
| Nil | 24.9% | 3.8% | 0.16% | 2.5% | | 2.1% | 0.02% | 0.07% |
| Mech | 12.3% | 1.9% | 0.08% | 1.2% | | 2.1% | 0.02% | 0.07% |
| Mech+LMWH | 7.1% | 1.1% | 0.04% | 0.7% | | 3.0% | 0.03% | 0.10% |
| Mech+Fon | 3.7% | 0.6% | 0.02% | 0.4% | | 4.7% | 0.05% | 0.16% |

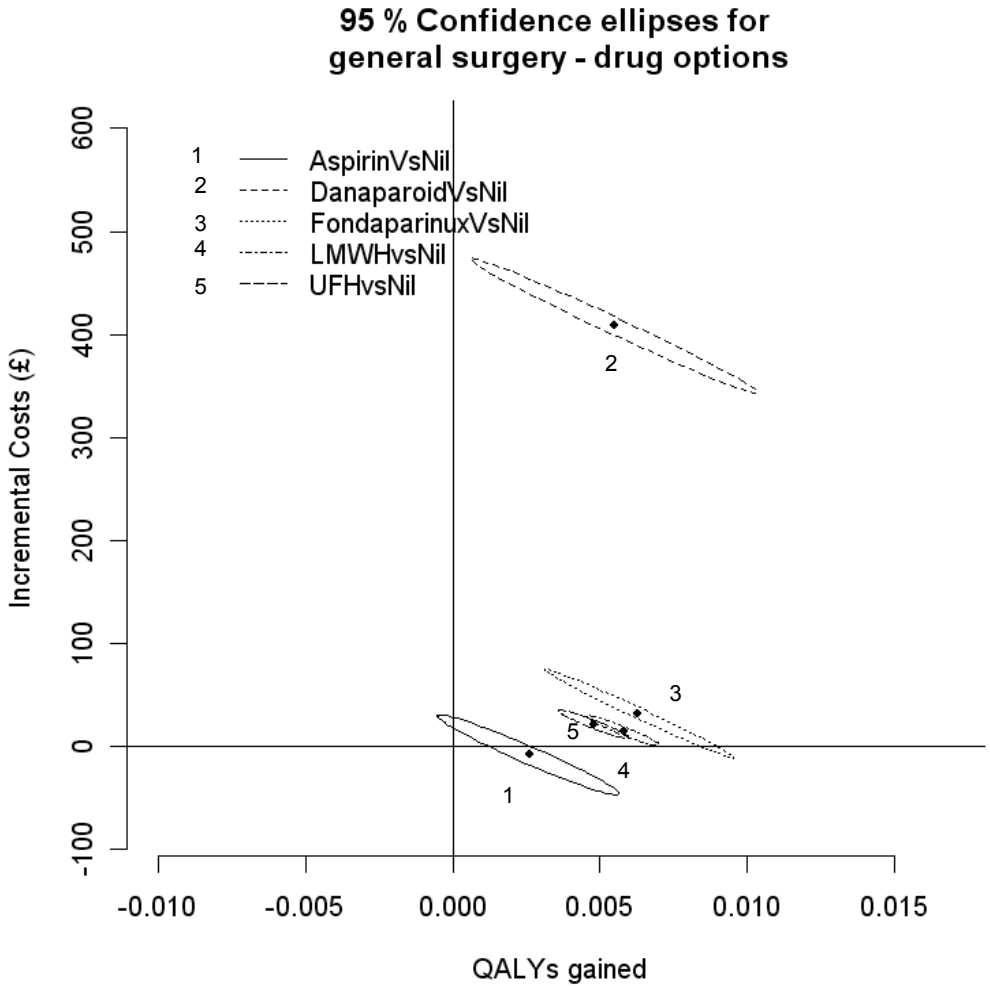
* Mech=mechanical prophylaxis, LMWH=low molecular weigh heparin, Fon=fondaparinux

**Table 12: Cost-effectiveness of combination prophylaxis – general surgery patient**

| Strategy | QALYs gained per patient compared with Nil | Incremental cost per patient compared with Nil | Incremental net benefit per patient compared with Nil |
|---|---|---|---|
| Nil | - | £0 | £0 |
| Mech | 0.0064 | -£6 | £133 |
| Mech+LMWH | 0.0080 | £36 | £125 |
| Mech+Fon | 0.0081 | £55 | £108 |

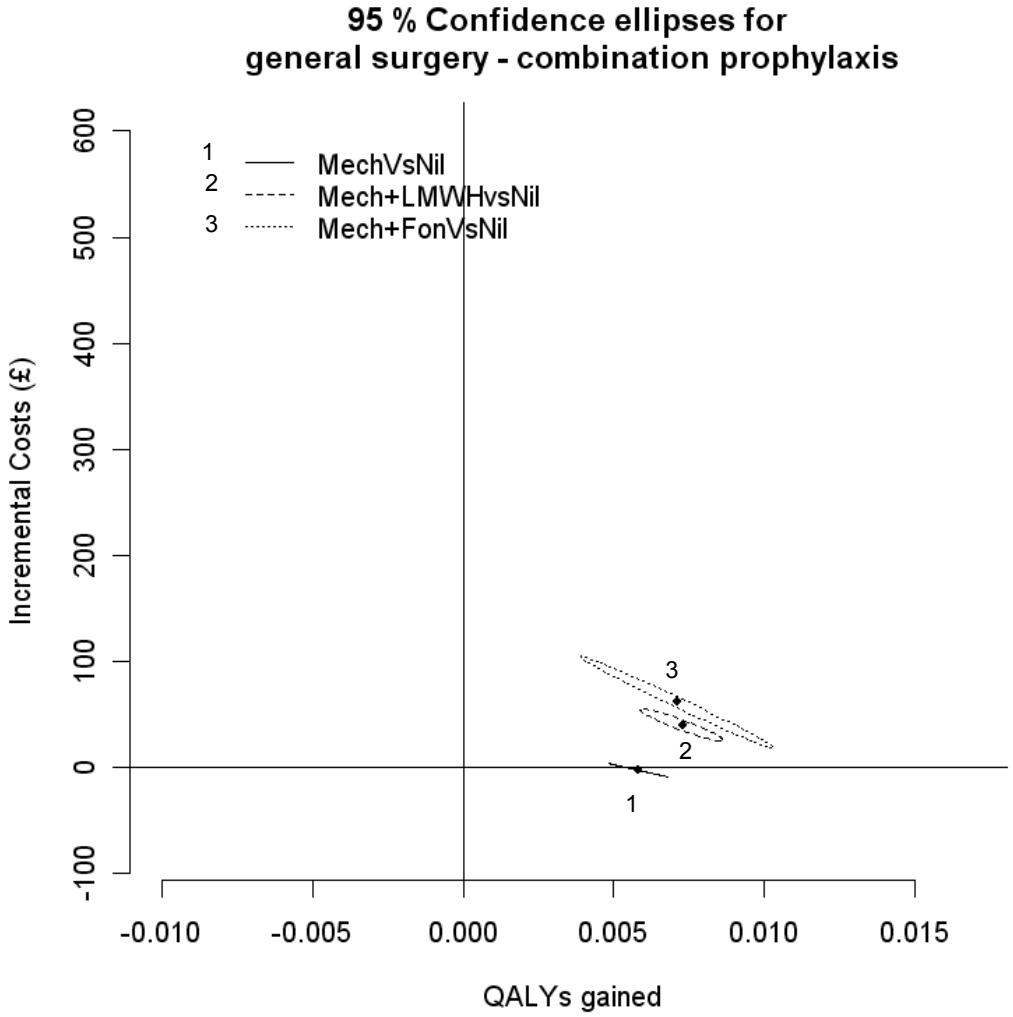
* Mech=mechanical prophylaxis, LMWH=low molecular weigh heparin, Fon=fondaparinux

**Diagram 6: Cost-effectiveness of drug-only prophylaxis – general surgery patient**




* For clarity of presentation warfarin has been omitted from this diagram. It's confidence ellipse overlapped substantially with the ellipse for UFH.

**Diagram 8: Cost-effectiveness of combined prophylaxis – general surgery patient**



## 13.3 *In-hospital prophylaxis: results by type of surgery*

Table 13 shows the proportion of times each drug strategy is optimal (most cost-effective), by type of surgery. (Each row adds up to 100%; the shaded cells indicate the most probable optimal strategy for each type of surgery). For hip fracture and elective hip, the evidence was quite convincing in favour of fondaparinux. For the two types of general surgery, there was more uncertainty but fondaparinux was optimal more times than other drugs. For hysterectomy, because of the low DVT risk and high bleeding risk, no-drug and aspirin were preferred over the other drug-only strategies.

Table 14 shows the proportion of times each strategy is optimal (From a subset of nil, mechanical, mechanical + LMWH, mechanical + fondaparinux), by type of surgery. For hip fracture and elective hip surgery, combination prophylaxis was cost-effective in the majority of simulations. For hysterectomy and the general surgery patient, combination prophylaxis was not cost-effective in the majority of simulations.

**Knee replacement surgery**

We have not developed a model specific to elective knee surgery because we do not have enough trials of such patients with a no prophylaxis arm to estimate the risk of PE in this patient group. But we know that patients from this group share very similar characteristics to elective hip surgery patients in terms of age, mortality, etc[134,390]. Their risk of PE is thought to be lower however - perhaps two thirds of that of elective hip patients[248]. If this is the case then we would expect to find that combination prophylaxis is cost-effective for knee replacement surgery but with less certainty than for hip replacement surgery.

**Table 13: Probabilistic sensitivity analysis for drug-only strategies**

| | Nil | Aspirin | Danaparoid | Fondaparinux | LMWH | UFH | OAC-adj |
|---|---|---|---|---|---|---|---|
| **Hip fracture** | 0% | 0% | 0% | 95% | 5% | 0% | 0% |
| **Elective hip** | 0% | 3% | 0% | 73% | 22% | 1% | 0% |
| **Hyster-ectomy** | 27% | 59% | 0% | 3% | 6% | 1% | 4% |
| **General surgery** | 0% | 14% | 0% | 45% | 36% | 3% | 1% |

* OAC-adj=adjustable-dose oral anticoagulants, LMWH=low molecular weigh heparin, UFH=unfractionated heparin

**Table 14: Probabilistic sensitivity analysis for mechanical and combination prophylaxis**

| | Nil | Mechanical | Mechanical +LMWH | Mechanical +Fondaparinux |
|---|---|---|---|---|
| **Hip fracture** | 0% | 4% | 12% | 84% |
| **Elective hip** | 0% | 29% | 24% | 48% |
| **Hyster-ectomy** | 30% | 69% | 1% | 1% |
| **General surgery** | 0% | 61% | 19% | 20% |

## 13.4 *In-hospital prophylaxis: sensitivity analyses*

Table 15 shows how the most cost-effective strategy (From the subset: nil, mechanical, mechanical + LMWH, mechanical + fondaparinux) varies as the baseline risk of major bleeding and DVT varies. For the purposes of this table it is assumed that (other than baseline risk), the patient shares the characteristics of the general surgery patient and that symptomatic PEs are in fixed proportion to DVTs (10.5:100). The lowest of the shaded cells (blue) indicates the baseline risk associated with elective hip surgery, as estimated from our RCTs. The uppermost of the shaded cells (green) indicates the baseline risk for gynaecological surgery patients and the middle shaded cell (yellow) indicates general surgery. It shows that on the basis of these risks, mechanical only is optimal for the average general surgery patient but that it is right on the threshold at which combination prophylaxis becomes cost-effective.

We then looked at how this grid changes as we varied some of the important assumptions in the model.

In Table 16, we extended the options to include single-drug strategies as well as combination strategies. In a few cells where the bleeding rate is low, fondaparinux on its own becomes cost-effective. Otherwise the results are unaffected.

Table 17 illustrates all drug prices reduced by 50% to reflect the practice of drug companies subsidising the prices of drugs for hospitals. Also we assumed that the IPC is supplied rent-free, which is apparently the case according to one supplier (Huntleigh). The results did not vary much but for the average general surgery patient this could make combination prophylaxis cost-effective. A few stakeholders have informed us that the discount on LMWH is substantially greater than the discount on fondaparinux. On this basis Mechanical + LMWH becomes cost-effective at moderate risk levels and so could be cost-effective for general surgery patients (Table 18).

In our base case analysis the fatality rate from major bleeding was 1%. If this rate was higher say 5% (Table 19) then combination prophylaxis is much less cost-effective and might be inappropriate even for elective hip surgery.

Alternatively, if we made the assumption that prophylaxis has the same relative impact on post-thrombotic syndrome and symptomatic VTE recurrence, as it does on immediate VTEs, then combination prophylaxis would become much more cost-effective (Table 20).

If we excluded mechanical + fondaparinux as an option (Table 21) then mechanical + LMWH supplants it where it was optimal.

We tested the sensitivity of our results to see what happens when we assume that prophylaxis is effective at reducing the risk of non-fatal events but not fatal events. If the effectiveness of prophylaxis at reducing fatal events is reduced by 50% then mechanical prophylaxis remains cost-effective and so does combination at high levels of risk (Table 22). In fact even if it's not averting any fatal events mechanical prophylaxis remains cost-effective (not in table). However, there is evidence that drug prophylaxis (notably heparin) reduces fatal PE and other symptomatic PE by a similar extent as it does for DVT (Appendix G), although there is not such clear evidence for mechanical prophylaxis. If we assume that the relative risk reduction of mechanical prophylaxis on fatal PE was only half that of its relative risk reduction on DVT then combination prophylaxis would become cost-effective at much lower levels of VTE risk (Table 23).

In the base case analysis, we assumed that a fatal event did not add to treatment costs – it could even reduce them since length of stay could be shorter. However, for some patients there maybe considerable intensive care costs before death. As a sensitivity analysis, we costed the fatal events (PEs and major bleeding events) the same as for the

non-fatal ones but the results changed negligibly, since such events are rare (Table 24).

If we included the strategy of two mechanical methods then we would find this strategy is optimal for all but the lowest risk patients (Table 25). This is because there is no risk of bleeding and the evidence in the MTC meta-analysis showed it to be the most effective strategy at reducing DVTs based on the results of the RCT evidence. However, this data comes from a few small trials and the GDG did not consider this evidence to be robust.

If we include the costs of treating heparin-induced thrombocytopaenia (HIT) then our overall strategy remains the same but at some risk levels fondaparinux supplants LMWH (Table 26). (We assumed that a drug cost of £1200 would be attributed to 5% of UFH patients and 0.5% of LMWH patients).

**Table 15: Optimal strategy by baseline risk**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | Nil | Nil | Nil | Nil | Nil |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M | M | M | M | M |
| 20% | 2.1% | M | M | M | M | M |
| 25% | 2.6% | M+Fon | M | M | M | M |
| 30% | 3.2% | M+Fon | M+LMWH | M | M | M |
| 35% | 3.7% | M+Fon | M+Fon | M+LMWH | M | M |
| 40% | 4.2% | M+Fon | M+Fon | M+LMWH | M+LMWH | M |
| 45% | 4.7% | M+Fon | M+Fon | M+LMWH | M+LMWH | M+LMWH |
| 50% | 5.3% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 60% | 5.8% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 70% | 6.3% | M+Fon | M+Fon | M+Fon | M+Fon | M+LMWH |
| 80% | 6.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 90% | 7.4% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 100% | 7.9% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |

Options included: Nil, M=Mechanical, M+LMWH=Mechanical in combination with LMWH, M+Fon=Mechanical in combination with fondaparinux,
Patient characteristics are those of the general surgery patient (excepting baseline risk)
The symptomatic PE risk is taken to be at a constant 10.5% of the DVT rate.
The blue (lower) shaded cell indicates the baseline risk associated with elective hip surgery. The yellow (mid) shaded cell indicates the baseline risk associated with the general surgery patient. The green (top) shaded cell indicates the baseline risk associated with the hysterectomy patient.

**Table 16: Sensitivity analysis 1 – include single drug strategies in addition to combination strategies**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | Asp | Asp | Asp | Asp | Asp |
| 10% | 1.1% | M | M | M | M | Asp |
| 15% | 1.6% | M | M | M | M | M |
| 20% | 2.1% | Fon | M | M | M | M |
| 25% | 2.6% | Fon | M | M | M | M |
| 30% | 3.2% | Fon | Fon | M | M | M |
| 35% | 3.7% | Fon | Fon | M+LMWH | M | M |
| 40% | 4.2% | M+Fon | M+Fon | M+LMWH | M+LMWH | M |
| 45% | 4.7% | M+Fon | M+Fon | M+LMWH | M+LMWH | M+LMWH |
| 50% | 5.3% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 60% | 5.8% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 70% | 6.3% | M+Fon | M+Fon | M+Fon | M+Fon | M+LMWH |
| 80% | 6.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 90% | 7.4% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 100% | 7.9% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |

**Table 17: Sensitivity analysis 2 – assuming that drugs are discounted at 50% of the BNF price and IPC machines are supplied rent-free**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | M | M | M | M | M |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M | M | M | M | M |
| 20% | 2.1% | M+Fon | M | M | M | M |
| 25% | 2.6% | M+Fon | M+LMWH | M | M | M |
| 30% | 3.2% | M+Fon | M+Fon | M+LMWH | M | M |
| 35% | 3.7% | M+Fon | M+Fon | M+LMWH | M+LMWH | M |
| 40% | 4.2% | M+Fon | M+Fon | M+LMWH | M+LMWH | M+LMWH |
| 45% | 4.7% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 50% | 5.3% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 60% | 5.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+LMWH |
| 70% | 6.3% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 80% | 6.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 90% | 7.4% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 100% | 7.9% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |

**Table 18: Sensitivity analysis 3 – assuming that LMWH is discounted to 20% of the BNF price and IPC machines are supplied rent-free**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | M | M | M | M | M |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M+LMWH | M | M | M | M |
| 20% | 2.1% | M+LMWH | M+LMWH | M | M | M |
| 25% | 2.6% | M+LMWH | M+LMWH | M+LMWH | M | M |
| 30% | 3.2% | M+LMWH | M+LMWH | M+LMWH | M | M |
| 35% | 3.7% | M+Fon | M+LMWH | M+LMWH | M+LMWH | M |
| 40% | 4.2% | M+Fon | M+LMWH | M+LMWH | M+LMWH | M+LMWH |
| 45% | 4.7% | M+Fon | M+Fon | M+LMWH | M+LMWH | M+LMWH |
| 50% | 5.3% | M+Fon | M+Fon | M+LMWH | M+LMWH | M+LMWH |
| 60% | 5.8% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 70% | 6.3% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 80% | 6.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+LMWH |
| 90% | 7.4% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 100% | 7.9% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |

**Table 19: Sensitivity analysis 4 – assuming 5% of major bleeds are fatal (c.f. 1% in base case analysis)**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | Nil | Nil | Nil | Nil | Nil |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M | M | M | M | M |
| 20% | 2.1% | M | M | M | M | M |
| 25% | 2.6% | M | M | M | M | M |
| 30% | 3.2% | M | M | M | M | M |
| 35% | 3.7% | M+LMWH | M | M | M | M |
| 40% | 4.2% | M+LMWH | M | M | M | M |
| 45% | 4.7% | M+Fon | M | M | M | M |
| 50% | 5.3% | M+Fon | M+LMWH | M | M | M |
| 60% | 5.8% | M+Fon | M+LMWH | M | M | M |
| 70% | 6.3% | M+Fon | M+LMWH | M+LMWH | M | M |
| 80% | 6.8% | M+Fon | M+LMWH | M+LMWH | M+LMWH | M |
| 90% | 7.4% | M+Fon | M+Fon | M+LMWH | M+LMWH | M |
| 100% | 7.9% | M+Fon | M+Fon | M+LMWH | M+LMWH | M+LMWH |

**Table 20: Sensitivity analysis 5 – include the estimated impact on post-thrombotic syndrome and recurrence**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | M | M | M | M | M |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M+Fon | M+LMWH | M | M | M |
| 20% | 2.1% | M+Fon | M+Fon | M+LMWH | M+LMWH | M |
| 25% | 2.6% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 30% | 3.2% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 35% | 3.7% | M+Fon | M+Fon | M+Fon | M+Fon | M+LMWH |
| 40% | 4.2% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 45% | 4.7% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 50% | 5.3% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 60% | 5.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 70% | 6.3% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 80% | 6.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 90% | 7.4% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 100% | 7.9% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |

**Table 21: Sensitivity analysis 6 – exclude fondaparinux**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | Nil | Nil | Nil | Nil | Nil |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M | M | M | M | M |
| 20% | 2.1% | M | M | M | M | M |
| 25% | 2.6% | M+LMWH | M | M | M | M |
| 30% | 3.2% | M+LMWH | M+LMWH | M | M | M |
| 35% | 3.7% | M+LMWH | M+LMWH | M+LMWH | M | M |
| 40% | 4.2% | M+LMWH | M+LMWH | M+LMWH | M+LMWH | M |
| 45% | 4.7% | M+LMWH | M+LMWH | M+LMWH | M+LMWH | M+LMWH |
| 50% | 5.3% | M+LMWH | M+LMWH | M+LMWH | M+LMWH | M+LMWH |
| 60% | 5.8% | M+LMWH | M+LMWH | M+LMWH | M+LMWH | M+LMWH |
| 70% | 6.3% | M+LMWH | M+LMWH | M+LMWH | M+LMWH | M+LMWH |
| 80% | 6.8% | M+LMWH | M+LMWH | M+LMWH | M+LMWH | M+LMWH |
| 90% | 7.4% | M+LMWH | M+LMWH | M+LMWH | M+LMWH | M+LMWH |
| 100% | 7.9% | M+LMWH | M+LMWH | M+LMWH | M+LMWH | M+LMWH |

**Table 22: Sensitivity analysis 7 – assuming each prophylaxis strategy is only half as effective at reducing fatal PEs compared with DVTs**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | Nil | Nil | Nil | Nil | Nil |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M | M | M | M | M |
| 20% | 2.1% | M | M | M | M | M |
| 25% | 2.6% | M | M | M | M | M |
| 30% | 3.2% | M | M | M | M | M |
| 35% | 3.7% | M+Fon | M | M | M | M |
| 40% | 4.2% | M+Fon | M | M | M | M |
| 45% | 4.7% | M+Fon | M+LMWH | M | M | M |
| 50% | 5.3% | M+Fon | M+LMWH | M | M | M |
| 60% | 5.8% | M+Fon | M+Fon | M+LMWH | M | M |
| 70% | 6.3% | M+Fon | M+Fon | M+LMWH | M+LMWH | M+LMWH |
| 80% | 6.8% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 90% | 7.4% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 100% | 7.9% | M+Fon | M+Fon | M+Fon | M+Fon | M+LMWH |

**Table 23: Sensitivity analysis 8 – assuming mechanical prophylaxis is only half as effective at reducing fatal PEs compared with DVTs**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | Nil | Nil | Nil | Nil | Nil |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M | M | M | M | M |
| 20% | 2.1% | M+Fon | M | M | M | M |
| 25% | 2.6% | M+Fon | M+LMWH | M+LMWH | M | M |
| 30% | 3.2% | M+Fon | M+LMWH | M+LMWH | M+LMWH | M |
| 35% | 3.7% | M+Fon | M+Fon | M+LMWH | M+LMWH | M+LMWH |
| 40% | 4.2% | M+Fon | M+Fon | M+LMWH | M+LMWH | M+LMWH |
| 45% | 4.7% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 50% | 5.3% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 60% | 5.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+LMWH |
| 70% | 6.3% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 80% | 6.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 90% | 7.4% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 100% | 7.9% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |

**Table 24: Sensitivity analysis 9 – attributing the same treatment cost to fatal events as for non-fatal events**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | Nil | Nil | Nil | Nil | Nil |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M | M | M | M | M |
| 20% | 2.1% | M | M | M | M | M |
| 25% | 2.6% | M+Fon | M | M | M | M |
| 30% | 3.2% | M+Fon | M+LMWH | M | M | M |
| 35% | 3.7% | M+Fon | M+Fon | M+LMWH | M | M |
| 40% | 4.2% | M+Fon | M+Fon | M+LMWH | M+LMWH | M |
| 45% | 4.7% | M+Fon | M+Fon | M+LMWH | M+LMWH | M+LMWH |
| 50% | 5.3% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 60% | 5.8% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 70% | 6.3% | M+Fon | M+Fon | M+Fon | M+Fon | M+LMWH |
| 80% | 6.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 90% | 7.4% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 100% | 7.9% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |

**Table 25: Sensitivity analysis 10 – allowing double mechanical prophylaxis as an option**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | Nil | Nil | Nil | Nil | Nil |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M+M | M+M | M+M | M+M | M+M |
| 20% | 2.1% | M+M | M+M | M+M | M+M | M+M |
| 25% | 2.6% | M+M | M+M | M+M | M+M | M+M |
| 30% | 3.2% | M+M | M+M | M+M | M+M | M+M |
| 35% | 3.7% | M+M | M+M | M+M | M+M | M+M |
| 40% | 4.2% | M+M | M+M | M+M | M+M | M+M |
| 45% | 4.7% | M+Fon | M+M | M+M | M+M | M+M |
| 50% | 5.3% | M+Fon | M+M | M+M | M+M | M+M |
| 60% | 5.8% | M+Fon | M+M | M+M | M+M | M+M |
| 70% | 6.3% | M+Fon | M+M | M+M | M+M | M+M |
| 80% | 6.8% | M+Fon | M+Fon | M+M | M+M | M+M |
| 90% | 7.4% | M+Fon | M+Fon | M+M | M+M | M+M |
| 100% | 7.9% | M+Fon | M+Fon | M+M | M+M | M+M |

*M=Mechanical, M+M=two types of mechanical used in combination (i.e. stockings and either intermittent pneumatic compression or foot impulse device)

**Table 26: Sensitivity analysis 11 – including treatment costs for HIT**

| DVT Risk | Symptomatic PE Risk | Major bleeding risk | | | | |
|---|---|---|---|---|---|---|
| | | 1% | 2% | 3% | 4% | 5% |
| 5% | 0.5% | Nil | Nil | Nil | Nil | Nil |
| 10% | 1.1% | M | M | M | M | M |
| 15% | 1.6% | M | M | M | M | M |
| 20% | 2.1% | M | M | M | M | M |
| 25% | 2.6% | M+Fon | M | M | M | M |
| 30% | 3.2% | M+Fon | M+Fon | M | M | M |
| 35% | 3.7% | M+Fon | M+Fon | M+LMWH | M | M |
| 40% | 4.2% | M+Fon | M+Fon | M+LMWH | M | M |
| 45% | 4.7% | M+Fon | M+Fon | M+Fon | M+LMWH | M |
| 50% | 5.3% | M+Fon | M+Fon | M+Fon | M+LMWH | M+LMWH |
| 60% | 5.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+LMWH |
| 70% | 6.3% | M+Fon | M+Fon | M+Fon | M+Fon | M+LMWH |
| 80% | 6.8% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 90% | 7.4% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |
| 100% | 7.9% | M+Fon | M+Fon | M+Fon | M+Fon | M+Fon |

## 13.5 *Post-discharge prophylaxis*

Table 27 shows the number of events occurring in the post-discharge period according to whether patients have post-discharge prophylaxis. Table 28 shows the incremental costs and effects associated with continued drug prophylaxis in the post-discharge period for the general surgery patient. At £77,000 and at £125,000 per QALY gained respectively neither LMWH nor fondaparinux is cost-effective, since the incidence of symptomatic PE is low, and the prophylaxis cost is high. For elective hip patients and the general surgery patient, the vast majority of simulations showed that post-discharge prophylaxis was not cost-effective (Table 29). However, for the hip fracture surgery which has a higher incidence of *fatal* pulmonary embolism extended prophylaxis was cost-effective in 60% of simulations.

Table 30 shows how the optimal strategy varies by baseline risk of VTE and baseline risk of major bleeding. Only with an incidence of symptomatic pulmonary embolism of 3.5% or above is post-discharge prophylaxis cost-effective. While studies show that the majority of symptomatic pulmonary embolisms are diagnosed after discharge, the post-discharge incidence still seems to be less than 1%[63,555] – even lower than our RCT evidence would suggest. Extended drug prophylaxis is sometimes recommended for cancer patients undergoing surgery but for the two trials of post-discharge LMWH prophylaxis[43,436], the incidence of PE was less than 1%, implying that extended drug prophylaxis is not cost-effective for this group.

Table 31 shows how the results change if both drug prices are discounted to about 50%. If prices are reduced to 40% of their BNF price then post-discharge prophylaxis becomes cost-effective for the elective hip patients (Table 32).

Table 33, we can see that the results are not very sensitive to the fatality rate associated with major bleeding. Table 34 shows that if we attribute a reduction in PTS and recurrence then extended prophylaxis is likely to be cost-effective for the elective hip patient and the general surgery patient. The BCSH guidance on diagnosis and treatment of heparin induced thrombocytopaenia (HIT) recommends carrying out a series of platelet counts up to day 14 to test for HIT[285]. Table 35 shows the results after adding the cost of a district nurse visit and full blood count to the LMWH strategy – the result is that for some risk levels where LMWH was optimal, fondaparinux becomes optimal instead.

*Post-discharge use of graduated compression stockings*

The cost-effectiveness of stockings post-discharge is difficult to assess and has not been modelled. The use of stockings post-discharge by patients, who are willing and able to comply with their recommended usage, is likely to be cost-effective (although spare pairs of stockings would need to be supplied). In patients who find it difficult to comply, including those with arthritis, implementation might require twice daily visits by a district nurse, which would considerably add to costs. Such usage might still be cost-effective but we do not know the magnitude of effectiveness of extended stocking use; the trial evidence for stocking use being only for the in-hospital period.

**Table 27: Events in post-discharge period, by type of prophylaxis in post-discharge period – general surgery patient**

| | All DVT | Sympto-matic DVT | Fatal PE | Sympto-matic PE non-fatal | | All Major bleed | Fatal Bleed | Stroke |
|---|---|---|---|---|---|---|---|---|
| Nil | 12.5% | 1.9% | 0.039% | 0.6% | | 0.1% | 0.00% | 0.00% |
| LMWH | 6.0% | 0.9% | 0.019% | 0.3% | | 0.4% | 0.00% | 0.01% |
| Fondaparinux | 0.5% | 0.1% | 0.002% | 0.0% | | 1.8% | 0.02% | 0.06% |

**Table 28: Cost-effectiveness of post-discharge prophylaxis - general surgery patient**

| Strategy (post-discharge) | QALYs gained per patient compared with Nil | Incremental cost per patient compared with Nil | Incremental net benefit per patient compared with Nil |
|---|---|---|---|
| Nil | - | £0 | £0 |
| LMWH | 0.0014 | £106 | -£78 |
| Fondaparinux | 0.0014 | £173 | -£146 |

**Table 29: Probabilistic sensitivity analysis for prophylaxis post-discharge**

| | No prophylaxis post-discharge | Extended LMWH | Extended fondaparinux |
|---|---|---|---|
| Hip fracture | 32% | 12% | 56% |
| Elective hip | 89% | 2% | 8% |
| General surgery | 99% | 0% | 1% |

**Table 30: Optimal strategy by post-discharge baseline risk**

| DVT post-discharge | Symptomatic PE post-discharge | Major bleeding post-discharge | | | | |
|---|---|---|---|---|---|---|
| | | 0.10% | 0.15% | 0.20% | 0.40% | 0.60% |
| 2.5% | 0.26% | Nil | Nil | Nil | Nil | Nil |
| 5.0% | 0.53% | Nil | Nil | Nil | Nil | Nil |
| 7.5% | 0.79% | Nil | Nil | Nil | Nil | Nil |
| 10.0% | 1.05% | Nil | Nil | Nil | Nil | Nil |
| 12.5% | 1.31% | Nil | Nil | Nil | Nil | Nil |
| 15.0% | 1.58% | Nil | Nil | Nil | Nil | Nil |
| 17.5% | 1.84% | Nil | Nil | Nil | Nil | Nil |
| 20.0% | 2.10% | Nil | Nil | Nil | Nil | Nil |
| 22.5% | 2.36% | Nil | Nil | Nil | Nil | Nil |
| 25.0% | 2.63% | Nil | Nil | Nil | Nil | Nil |
| 30.0% | 3.15% | Nil | Nil | Nil | Nil | Nil |
| 35.0% | 3.68% | Fon | LMWH | LMWH | Nil | Nil |
| 40.0% | 4.20% | Fon | Fon | LMWH | LMWH | Nil |
| 45.0% | 4.73% | Fon | Fon | Fon | LMWH | LMWH |
| 50.0% | 5.25% | Fon | Fon | Fon | LMWH | LMWH |

Options included: Nil, LMWH, Fon=fondaparinux,
Patient characteristics are those of the general surgery patient (excepting for post-discharge risk)
The symptomatic PE risk is taken to be at a constant of the DVT rate.
The blue (lower) shaded cell indicates the baseline risk associated with elective hip surgery. The yellow (mid) shaded cell indicates the baseline risk associated with the general surgery patient.

**Table 31: Post-discharge sensitivity analysis 1 – assuming that both drugs are discounted to 50% of the BNF price**

| DVT post-discharge | Symptomatic PE post-discharge | Major bleeding post-discharge | | | | |
|---|---|---|---|---|---|---|
| | | 0.10% | 0.15% | 0.20% | 0.40% | 0.60% |
| 2.5% | 0.26% | Nil | Nil | Nil | Nil | Nil |
| 5.0% | 0.53% | Nil | Nil | Nil | Nil | Nil |
| 7.5% | 0.79% | Nil | Nil | Nil | Nil | Nil |
| 10.0% | 1.05% | Nil | Nil | Nil | Nil | Nil |
| 12.5% | 1.31% | Nil | Nil | Nil | Nil | Nil |
| 15.0% | 1.58% | Nil | Nil | Nil | Nil | Nil |
| 17.5% | 1.84% | Nil | Nil | Nil | Nil | Nil |
| 20.0% | 2.10% | Nil | Nil | Nil | Nil | Nil |
| 22.5% | 2.36% | Fon | Nil | Nil | Nil | Nil |
| 25.0% | 2.63% | Fon | LMWH | LMWH | Nil | Nil |
| 30.0% | 3.15% | Fon | Fon | LMWH | LMWH | Nil |
| 35.0% | 3.68% | Fon | Fon | Fon | LMWH | LMWH |
| 40.0% | 4.20% | Fon | Fon | Fon | LMWH | LMWH |
| 45.0% | 4.73% | Fon | Fon | Fon | LMWH | LMWH |
| 50.0% | 5.25% | Fon | Fon | Fon | LMWH | LMWH |

**Table 32: Post-discharge sensitivity analysis 2 – assuming that LMWH is discounted to 20% of the BNF price**

| DVT post-discharge | Symptomatic PE post-discharge | Major bleeding post-discharge | | | | |
|---|---|---|---|---|---|---|
| | | 0.10% | 0.15% | 0.20% | 0.40% | 0.60% |
| 2.5% | 0.26% | Nil | Nil | Nil | Nil | Nil |
| 5.0% | 0.53% | Nil | Nil | Nil | Nil | Nil |
| 7.5% | 0.79% | Nil | Nil | Nil | Nil | Nil |
| 10.0% | 1.05% | Nil | Nil | Nil | Nil | Nil |
| 12.5% | 1.31% | Nil | Nil | Nil | Nil | Nil |
| 15.0% | 1.58% | Nil | Nil | Nil | Nil | Nil |
| 17.5% | 1.84% | LMWH | LMWH | LMWH | Nil | Nil |
| 20.0% | 2.10% | LMWH | LMWH | LMWH | Nil | Nil |
| 22.5% | 2.36% | LMWH | LMWH | LMWH | LMWH | Nil |
| 25.0% | 2.63% | LMWH | LMWH | LMWH | LMWH | LMWH |
| 30.0% | 3.15% | LMWH | LMWH | LMWH | LMWH | LMWH |
| 35.0% | 3.68% | LMWH | LMWH | LMWH | LMWH | LMWH |
| 40.0% | 4.20% | LMWH | LMWH | LMWH | LMWH | LMWH |
| 45.0% | 4.73% | LMWH | LMWH | LMWH | LMWH | LMWH |
| 50.0% | 5.25% | LMWH | LMWH | LMWH | LMWH | LMWH |

**Table 33: Post-discharge sensitivity analysis 3 – assuming 5% of major bleeds are fatal (c.f. 1% in base case analysis)**

| DVT post-discharge | Symptomatic PE post-discharge | Major bleeding post-discharge | | | | |
|---|---|---|---|---|---|---|
| | | 0.10% | 0.15% | 0.20% | 0.40% | 0.60% |
| 2.5% | 0.26% | Nil | Nil | Nil | Nil | Nil |
| 5.0% | 0.53% | Nil | Nil | Nil | Nil | Nil |
| 7.5% | 0.79% | Nil | Nil | Nil | Nil | Nil |
| 10.0% | 1.05% | Nil | Nil | Nil | Nil | Nil |
| 12.5% | 1.31% | Nil | Nil | Nil | Nil | Nil |
| 15.0% | 1.58% | Nil | Nil | Nil | Nil | Nil |
| 17.5% | 1.84% | Nil | Nil | Nil | Nil | Nil |
| 20.0% | 2.10% | Nil | Nil | Nil | Nil | Nil |
| 22.5% | 2.36% | Nil | Nil | Nil | Nil | Nil |
| 25.0% | 2.63% | Nil | Nil | Nil | Nil | Nil |
| 30.0% | 3.15% | Nil | Nil | Nil | Nil | Nil |
| 35.0% | 3.68% | Nil | Nil | Nil | Nil | Nil |
| 40.0% | 4.20% | LMWH | LMWH | Nil | Nil | Nil |
| 45.0% | 4.73% | LMWH | LMWH | LMWH | Nil | Nil |
| 50.0% | 5.25% | Fon | LMWH | LMWH | Nil | Nil |

**Table 34: Post-discharge sensitivity analysis 4 – include the estimated impact on post-thrombotic syndrome and recurrence**

| DVT post-discharge | Symptomatic PE post-discharge | Major bleeding post-discharge | | | | |
|---|---|---|---|---|---|---|
| | | 0.10% | 0.15% | 0.20% | 0.40% | 0.60% |
| 2.5% | 0.26% | Nil | Nil | Nil | Nil | Nil |
| 5.0% | 0.53% | Nil | Nil | Nil | Nil | Nil |
| 7.5% | 0.79% | Nil | Nil | Nil | Nil | Nil |
| 10.0% | 1.05% | LMWH | LMWH | LMWH | Nil | Nil |
| 12.5% | 1.31% | Fon | Fon | LMWH | LMWH | LMWH |
| 15.0% | 1.58% | Fon | Fon | Fon | LMWH | LMWH |
| 17.5% | 1.84% | Fon | Fon | Fon | LMWH | LMWH |
| 20.0% | 2.10% | Fon | Fon | Fon | LMWH | LMWH |
| 22.5% | 2.36% | Fon | Fon | Fon | Fon | LMWH |
| 25.0% | 2.63% | Fon | Fon | Fon | Fon | LMWH |
| 30.0% | 3.15% | Fon | Fon | Fon | Fon | Fon |
| 35.0% | 3.68% | Fon | Fon | Fon | Fon | Fon |
| 40.0% | 4.20% | Fon | Fon | Fon | Fon | Fon |
| 45.0% | 4.73% | Fon | Fon | Fon | Fon | Fon |
| 50.0% | 5.25% | Fon | Fon | Fon | Fon | Fon |

**Table 35: Post-discharge sensitivity analysis 5 – include full blood count testing after discharge**

| DVT post-discharge | Symptomatic PE post-discharge | Major bleeding post-discharge | | | | |
|---|---|---|---|---|---|---|
| | | 0.10% | 0.15% | 0.20% | 0.40% | 0.60% |
| 2.5% | 0.26% | Nil | Nil | Nil | Nil | Nil |
| 5.0% | 0.53% | Nil | Nil | Nil | Nil | Nil |
| 7.5% | 0.79% | Nil | Nil | Nil | Nil | Nil |
| 10.0% | 1.05% | Nil | Nil | Nil | Nil | Nil |
| 12.5% | 1.31% | Nil | Nil | Nil | Nil | Nil |
| 15.0% | 1.58% | Nil | Nil | Nil | Nil | Nil |
| 17.5% | 1.84% | Nil | Nil | Nil | Nil | Nil |
| 20.0% | 2.10% | Nil | Nil | Nil | Nil | Nil |
| 22.5% | 2.36% | Nil | Nil | Nil | Nil | Nil |
| 25.0% | 2.63% | Nil | Nil | Nil | Nil | Nil |
| 30.0% | 3.15% | Nil | Nil | Nil | Nil | Nil |
| 35.0% | 3.68% | Fon | Fon | Nil | Nil | Nil |
| 40.0% | 4.20% | Fon | Fon | Fon | Nil | Nil |
| 45.0% | 4.73% | Fon | Fon | Fon | LMWH | Nil |
| 50.0% | 5.25% | Fon | Fon | Fon | LMWH | LMWH |

## 13.6 *Conclusions and Recommendations*

### 13.6.1 General conclusions

Mechanical prophylaxis is cost-effective compared with no prophylaxis even at low risk of VTE. At low levels of VTE risk or high levels of major bleeding mechanical prophylaxis is more cost-effective than drug prophylaxis.

Taking into account the results of the direct comparisons and patient views (chapter 5), the mixed treatment comparisons (chapter 12) and the cost effectiveness analysis (this chapter) the GDG recommended that graduated compression stockings be offered to all patients having major surgery because they are suitable for use in theatre, on the ward and at home. There was no evidence of a difference in effectiveness between the different mechanical compression methods (chapter 5 and 12) and therefore the GDG recommended that IPC devices or foot pumps could be used as an alternative whilst patients were in hospital.

The cost-effectiveness of combination therapy (a drug combined with a mechanical device) is dependent on baseline risk of major bleeding as well as the baseline risk of VTE. Fondaparinux or LMWH are the drugs of choice in the majority of scenarios.

### 13.6.2 Implications for specific types of surgery

For recommendations specific to type of surgery – see Chapter 14.

1. For **hip surgery**, mechanical + fondaparinux is the most cost-effective option (although this is contingent on the relative reduction in fatal and other symptomatic pulmonary embolism being similar to the relative reduction in DVT, one of our key assumptions). For hip fracture surgery, it is cost-effective to extend prophylaxis 4 weeks beyond surgery because of the high incidence of *fatal* pulmonary embolism. For elective hip surgery, it is only cost-effective if patients have additional VTE risk factors.

2. For **general surgery**, combination prophylaxis was not cost-effective in our base case analysis but there is more uncertainty as it is near the boundary of cost-effectiveness. Therefore for patients with additional VTE risk factors, combination prophylaxis is likely to be cost-effective.

3. For **gynaecological surgery**, the combination prophylaxis is unlikely to be cost-effective given the apparently low VTE rate and high major bleeding rate. The high incidence of major bleeding occurring in our trial data may not be representative though. A study of more than 32,000 hysterectomies indicated a much lower complication rate[365]. However, the relatively low incidence of symptomatic VTEs in gynaecological surgery has been noted elsewhere[564].

4. For **neurological surgery**, we did not have an estimate of the risk of major bleeding but given that most major bleeding occurs at site of surgery, there is potentially a great deal of extra morbidity associated with drugs. In this particular case, the combination of prophylaxis may not be as cost-effective, even though patients may be at high risk.

We should be cautious about comparing different types of surgery. Firstly, the categories are very broad and heterogeneous; it could be that there is more variation within each category than there is between categories. We have made the assumption that the relative risks are constant regardless of baseline risk / type surgery; this is less likely to be the case if baseline risk is either very high or very low. We have inadequate data on the baseline risk for neurological, vascular, urological, cardiology and thoracic surgery, especially for major bleeding

We did not test our assumption that relative effect size is constant regardless of baseline risk or type of surgery. Our conclusions for major orthopaedic and major general surgery are unlikely to be challenged since there is a great deal of evidence for these categories (Chapters 5-10). However, for other categories of surgery, where there was little evidence, our recommendations are highly dependent on this assumption.

Three previously published economic evaluations have found extended prophylaxis to be cost-effective for elective hip surgery patients[62,125,209]. However, none included the consequences of major bleeding, one included PTS and recurrence in their base case analysis. Furthermore one study was set in Switzerland, where the high treatment cost savings are unlikely to be transferable to the NHS and one had a post-discharge risk of symptomatic PE that is substantially higher than our estimates (Chapter 4)

### 13.6.3 Implications for patients with additional risk factors

If a particular patient characteristic raises their risk of VTE, other things remaining equal, it could mean that combination prophylaxis becomes cost-effective. However, if the characteristic also affects other variables then this might not necessarily be the case.

In the cases of old age or cancer, studies have shown that these patients have a higher baseline risk of VTE implying *increased* capacity to benefit. However, they also have lower life expectancy implying *reduced* capacity to benefit. If these patients are at a higher baseline risk of major bleeding then their capacity to benefit from drug/combination prophylaxis would be further reduced. In this case combination prophylaxis might not be as cost-effective even though the baseline risk is high.

The impact of individual patient risk factors is difficult to evaluate, especially when the evidence comes from a variety of groups, some surgical and some non-surgical (Chapter 4). For this reason, the Guideline Development Group took the pragmatic approach of assuming that a single individual patient risk factor would be enough to make combined prophylaxis optimal for patients undergoing major surgery. Likewise, it was assumed that a single individual patient risk factor would be enough to make extended prophylaxis optimal for patients undergoing elective hip surgery.

### 13.6.4 Sensitivity analyses

The results were very sensitive (therefore less robust) to some of the assumptions used to populate the model:

- the assumption of 5% fatality amongst major bleeds (instead of 1%) was associated with the combination prophylaxis being much less cost effective

- the inclusion of PTS and recurrence was associated with combination prophylaxis and extended prophylaxis being much more cost-effective

- the assumption of reduced effectiveness for mechanical methods in preventing fatal PE meant that combination prophylaxis is more cost-effective

- cost-effectiveness was sensitive to the discounting of drug prices, especially in the post-discharge period..

### 13.6.5 Recommendations

**Inpatients having surgery should be offered thigh-length graduated compression/anti-embolism stockings from the time of admission to hospital unless contraindicated (for example, in patients with established peripheral arterial disease or diabetic neuropathy). If thigh-length stockings are inappropriate for a particular patient for reasons of compliance or fit, knee-length stockings may be used as a suitable alternative.**

**Intermittent pneumatic compression or foot impulse devices may be used as alternatives or in addition to graduated compression/anti-embolism stockings while surgical patients are in hospital.**

**In addition to mechanical prophylaxis, patients at increased risk of VTE because they have individual risk factors (see box 1) and patients having orthopaedic surgery should be offered low molecular weight heparin (LMWH). Fondaparinux, within its licensed indications, may be used as an alternative to LMWH.**

See chapter 14 for recommendations relating to specific surgical specialities.

### 13.6.6 Future research

The absolute effectiveness and cost-effectiveness of different strategies is highly dependent on the patient's baseline risk of symptomatic VTE and of major bleeding. Our analysis could be refined with better data on the risk levels of different patient groups. Validated risk models that incorporate specific types of surgery (not just broad categories), types of anaesthesia, length of stay and patient-specific risk factors would be invaluable.

Conventionally, prophylaxis is either until discharge or for 4-5 weeks post surgery but the optimal strategy for some patient groups might be somewhere in between. It would be useful to have data on the timing of events as well as the total risk.

Ideally, we would like precise estimates of the relative risks for non-fatal and fatal PE as well as for DVT but the size of the trials required would be prohibitively large. Longer-term follow-up of trials to assess impact of prophylaxis on longer-term outcomes (PTS and recurrence) would be invaluable, since the results are highly sensitive to their inclusion.

There have not been many trials that have evaluated two types of mechanical prophylaxis used in combinations. The few studies that have done so show this strategy to be as efficacious as drug-mechanical combinations. If these effects are real then double-mechanical strategy is easily the most effective and cost-effective strategy across all surgical groups because of the absence of an elevated bleeding risk. This strategy is promising but it would be incautious to recommend it without further evidence because not only are the studies small and few in number but also there is a worry that the use of mechanical devices other than stockings could make patients less mobile with the result of increasing rather than reducing VTEs.

# 14 Surgical Specialities

This chapter deals with the implications of our findings of clinical and cost effectiveness of prophylactic strategies for the different surgical specialities. We examine the factors that may alter ones choice of prophylaxis and the evidence in each of the surgical areas.

## 14.1 *Orthopaedic surgery*

This section covers inpatients undergoing orthopaedic surgery. Orthopaedic surgery is associated with a high risk of venous thromboembolism particularly in those patients undergoing total joint replacement or surgery for a fracture of the femoral neck. Because of this perceived increased risk of the development of venous thromboembolism in orthopaedic patients, there have been many studies addressing this issue. Although there is a general consensus that patients undergoing major orthopaedic surgery should be offered some form of prophylaxis, there is not a general consensus achieved as to the most effective method of prophylaxis.

### 14.1.1 Factors that may alter the choice of prophylaxis

Factors that might alter the risk of VTE

- Many patients undergoing surgery for femoral neck fracture are elderly and may have co-morbidities that increase the risk of developing deep vein thrombosis and pulmonary emboli.

Factors that increase the risk of bleeding or the hazard associated with it

- no specific factors

Other factors that may alter the choice of prophylaxis

- no specific factors

### 14.1.2 Evidence

The data for all RCTs were sub-grouped to determine if there was a difference between surgical specialities and the effectiveness of each method of prophylaxis. We did not find reliable statistical evidence to be certain of a difference. Consequently, to get a reliable estimate of effectiveness of different prophylaxis we analysed the RCTs for all surgical specialities together. The risk for developing a DVT varies depending on the baseline risk for each type of surgery and the patient specific risk factors.

We have estimated, from the incidence in the RCTs (Chapter 4), that the risk of developing deep vein thrombosis in orthopaedic surgery when not receiving thromboprophylaxis is:

- 44% (95%CI: 42% to 47%) for patients having elective hip surgery

- 37% (95%CI: 35% to 40%) for patients having surgery for hip fracture and

- 27% (95%CI: 22% to 32%) for patients having elective knee surgery.

Our model suggests that a mechanical method of prophylaxis (i.e. graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices) plus low molecular weight heparin or fondaparinux is cost effective in all patients undergoing orthopaedic surgery. It is also cost effective for all patients having surgery for hip fracture or patients having elective orthopaedic surgery who are at higher risk to have their drug prophylaxis continued for 4 weeks after surgery. For many patients, much of this time will occur after discharge and require patients/carers/family to inject their pharmacological agent. In our review, we found that 8% of patients need daily support with injections from a district nurse. Any patient already receiving a pharmacological agent not related to the surgery that acts as a prophylaxis may not need additional pharmacological prophylaxis.

### 14.1.3 Recommendations

Elective Orthopaedic Surgery

**Patients having elective orthopaedic surgery should be offered mechanical prophylaxis and either LMWH or fondaparinux.**

**Patients having hip replacement surgery with one or more risk factors for VTE (see box 1) should have their LMWH or fondaparinux therapy continued for 4 weeks after their surgery**

Hip Fracture

**Patients having surgery for hip fracture should be offered mechanical prophylaxis and either LMWH or fondaparinux.**

**LMWH or fondaparinux therapy should be continued for 4 weeks after hip fracture surgery.**

## 14.2 *General surgery*

This section covers inpatients undergoing general surgery. This includes both open and laparoscopic surgery. General surgery of its nature is heterogeneous in the age of patients, the pathological conditions being dealt with and organs and systems operated upon. There remain a variety of procedures retained within "general surgery" that are specialisations in themselves. These include upper gastrointestinal surgery and lower intestinal surgery (or coloproctology).

### 14.2.1 Factors that may alter the choice of prophylaxis

Factors that might alter the risk of VTE

- Patients having surgery for cancer will have a high risk of developing a DVT or pulmonary embolism.

- Patients having emergency procedures are often elderly and will consequently be at higher risk of developing a DVT or pulmonary embolism.

- Some patients having emergency procedures may already be using anticoagulation or antiplatelet therapy. This needs to be considered when deciding on the method of prophylaxis.

Factors that increase the risk of bleeding or the hazard associated with it

- Laparoscopic procedures may be associated with less bleeding than open surgery.

There are no other special factors that would affect the choice of, and use of, specific methods of prophylaxis in general surgery. Vascular surgery is considered in a separate section.

### 14.2.2 Evidence

There is some RCT evidence directly related to general surgery. The data for all RCTs were sub-grouped to determine if there was a difference by surgical speciality. We did not find reliable statistical evidence to be certain of a difference between surgical specialities in the effectiveness of any method of prophylaxis. Consequently, to get a reliable estimate of effectiveness of different prophylaxis we analysed the RCTs for all surgical specialities together. The risk for developing a DVT varies depending on the baseline risk for each type of surgery and the patient specific risk factors.

We have estimated, from the incidence in the RCTs (Chapter 4), that the risk of developing deep vein thrombosis in general surgery patients not receiving thromboprophylaxis is 24% (95%CI: 23% to 26%). Our model suggests that a mechanical method of prophylaxis (i.e. graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices) is cost effective in all patients undergoing general surgery. A mechanical method of prophylaxis plus low molecular weight heparin or fondaparinux is cost effective in patients at increased risk of venous thromboembolism.

### 14.2.3 Recommendations

**Patients having general surgery should be offered mechanical prophylaxis.**

**Patients having general surgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and either LMWH or fondaparinux.**

## 14.3 *Gynaecological surgery*

This section covers inpatients undergoing gynaecological surgery excluding caesarean section. This includes abdominal, vaginal and laparoscopic surgery.

### 14.3.1 Factors that may alter the choice of prophylaxis

Factors that might alter the risk of VTE

- Patients may be using hormonal contraception and hormone replacement therapy, which will increase their risk of developing a DVT or pulmonary embolism.

• Patients having surgery for cancer will have a high risk of developing a DVT or pulmonary embolism.

There are no special factors that increase the risk of bleeding or the hazard associated with it in gynaecological surgery.

There are no other special factors that would affect the choice of, and use of, specific methods of prophylaxis.

### 14.3.2 Evidence

There is some RCT evidence directly related to gynaecological surgery. The data for all RCTs were sub-grouped to determine if there was a difference by surgical speciality. We did not find reliable statistical evidence to be certain of a difference between surgical specialities in the effectiveness of any method of prophylaxis. Consequently, to get a reliable estimate of effectiveness of different prophylaxis we analysed the RCTs for all surgical specialities together. The risk for developing a DVT varies depending on the baseline risk for each type of surgery and the patient specific risk factors.

We have estimated, from the incidence in the RCTs (Chapter 4), that the risk of developing deep vein thrombosis in gynaecological surgery patients not receiving thromboprophylaxis is 16% (95%CI: 13% to 19%). Our model suggests that a mechanical method of prophylaxis (i.e. graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices) is cost effective in all patients undergoing gynaecological surgery. A mechanical device plus low molecular weight heparin is cost effective in patients at increased risk of venous thromboembolism. Fondaparinux in not licensed for use with these patients.

### 14.3.3 Recommendations

**Patients having gynaecological surgery should be offered mechanical prophylaxis.**

**Patients having gynaecological surgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LMWH.**

## 14.4 *Cardiac surgery*

This section covers patients undergoing cardiac surgery.

### 14.4.1 Factors that may alter the choice of prophylaxis

Factors that might alter the risk of VTE

• Full heparin anticoagulation is used during cardiopulmonary bypass which is typically one to two hours of a two to five hour surgery.

• Surgeries performed "off pump" (surgeries performed without the use of heart lung machines) are also covered by heparin anticoagulation.

• Most patients with coronary artery disease are given antiplatelet therapy up to shortly prior to surgery and it is recommenced soon after.

• Many patients with valve disease have warfarin anticoagulation.

• Patients in atrial fibrillation will generally have warfarin anticoagulation.

• All these pharmacological agents have the effect of reducing the risk of developing a DVT or pulmonary embolism.

Factors that increase the risk of bleeding or the hazard associated with it

• Patients receiving antiplatelet medication, heparin or warfarin will have an increased risk of bleeding.

Other factors that may alter the choice of prophylaxis

• Many of these patients have leg veins removed for use as grafts. This would preclude the use of both GCS and IPC during the surgery but they could be used after.

### 14.4.2 Evidence

There is little RCT evidence directly related to cardiac surgery. The data for all RCTs were sub-grouped to determine if there was a difference between surgical specialities and the effectiveness of each method of prophylaxis. We did not find reliable statistical evidence to be certain of a difference. Consequently, to get a reliable estimate of effectiveness of different prophylaxis we analysed the RCTs for all surgical specialities together. The risk for developing a DVT varies depending on the baseline risk for each type of surgery and the patient specific risk factors.

We have estimated, from the incidence in the RCTs (Chapter 4), that the risk of developing deep vein thrombosis for cardiac surgery patients not receiving thromboprophylaxis to be 14% (95%CI: 7 to 24%), although its ranking in among amongst other surgeries in our HES data would suggest that the risk could be higher. Our model suggests that a mechanical method of prophylaxis (i.e. graduated compression stockings, intermittent pneumatic

compression devices or foot impulse devices) is cost effective in all patients undergoing cardiac surgery. We believe that a mechanical device plus low molecular weight heparin is likely to be cost effective in patients at increased risk of venous thromboembolism. Any patient already receiving a pharmacological agent not related to the surgery that acts as a prophylaxis may not need additional pharmacological prophylaxis. Fondaparinux in not licensed for use with these patients.

### 14.4.3 Recommendations

**Patients having cardiac surgery should be offered mechanical prophylaxis.**

**Patients having cardiac surgery who are not otherwise receiving anticoagulation therapy and who have one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LMWH.**

## 14.5 *Thoracic surgery*

This section covers inpatients undergoing thoracic surgery.

### 14.5.1 Factors that may alter the choice of prophylaxis

Factors that might alter the risk of VTE

- After lung resection there is an anatomically reduced pulmonary vascular bed. Any pulmonary embolism that occurs in these patients is likely to carry much higher risk of death.

- Most patients having video-assisted thorascopic surgery (VATS), particularly for pneumothorax, are young (less than 30 years) and are able to walk around the ward up to the time of surgery and soon after and have short lengths of stay

- In the older age group there are patients in atrial fibrillation who will generally have warfarin anticoagulation.

There are no special factors that increase the risk of bleeding or the hazard associated with it in thoracic surgery.

There are no other special factors that would affect the choice of, and use of, specific methods of prophylaxis in thoracic surgery.

### 14.5.2 Evidence

There is little RCT evidence directly related to thoracic surgery. The data for all RCTs were sub-grouped to determine if there was a difference between surgical specialities and the effectiveness of each method of prophylaxis. We did not find reliable statistical evidence to be certain of a difference. Consequently, to get a reliable estimate of effectiveness of different prophylaxis we analysed the RCTs for all surgical specialities together. The risk for developing a DVT varies depending on the baseline risk for each type of surgery and the patient specific risk factors.

We did not have data, from the incidence in the RCTs (Chapter 4), that allowed us to estimate the risk of developing deep vein thrombosis in thoracic surgery patients not receiving thromboprophylaxis. However, according to our HES data, its ranking among other surgeries would suggest that the risk is high. Our model suggests that a mechanical method of prophylaxis (i.e. graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices) is cost effective even in patients at relatively moderate risk. We believe that a mechanical device plus low molecular weight heparin is likely to be cost-effective in patients at increased risk of venous thromboembolism. Fondaparinux in not licensed for use with these patients.

### 14.5.3 Recommendations

**Patients having thoracic surgery should be offered mechanical prophylaxis.**

**Patients having thoracic surgery with one or more ated risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LMWH.**

## 14.6 *Urological surgery*

This section covers inpatients undergoing urological surgery. The procedures can be divided into three groups: pelvic cancer surgery, renal surgery and laparoscopic and minimally invasive surgery. Patients undergoing these procedures are usually between the ages of 65 and 75. Laparoscopic procedures are becoming more common in preference to open surgery and have a lower risk of bleeding. However, there is some concern that the increased pressure in the peritoneum during laparoscopic surgery would cause venous stasis[269,490,573]. Laparoscopic procedures also tend to last longer than open urological procedures.

### 14.6.1 Factors that may alter the choice of prophylaxis

Factors that might alter the risk of VTE

- Many urological surgery patients get spinal and epidural anaesthesia. This may reduce the risk of developing a deep vein thrombosis.

Factors that increase the risk of bleeding or hazard associated with it

• Renal surgery procedures involve operating in the vicinity of the inferior vena cava which may be disrupted and increase the risk of DVT.

There are no other special factors that would affect the choice of, and use of, specific methods of prophylaxis in thoracic surgery.

### 14.6.2 Evidence

There is little RCT evidence directly related to urological surgery. The data for all RCTs were sub-grouped to determine if there was a difference between surgical specialities and the effectiveness of each method of prophylaxis. We did not find reliable statistical evidence to be certain of a difference. Consequently, to get a reliable estimate of effectiveness of different prophylaxis we analysed the RCTs for all surgical specialities together. The risk for developing a DVT varies depending on the baseline risk for each type of surgery and the patient specific risk factors.

We have estimated, from the incidence in the RCTs (Chapter 4), that the risk of developing deep vein thrombosis in urological surgery patients not receiving thromboprophylaxis is 10% (95%CI: 6% to 15%) , although its ranking in among amongst other surgeries in our HES data would suggest that the risk could be higher. Our model suggests that a mechanical method of prophylaxis (i.e. graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices) is cost effective even at relatively moderate risk. We believe a mechanical device plus low molecular weight heparin is likely to be cost effective in patients at increased risk of venous thromboembolism. Fondaparinux in not licensed for use with these patients.

### 14.6.3 Recommendations

**Patients having urological surgery should be offered mechanical prophylaxis.**

**Patients having urological surgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis plus LMWH.**

## 14.7 *Neurosurgery including spinal surgery*

This section covers inpatients undergoing neurosurgery. The majority would be less than 6 hours duration but there are some that would last longer. Procedures can be categorised into cranial and spinal, a large number of which are emergency cases. Neuroendovascular interventions are also covered by this section because such patients are generally admitted to neurosurgery wards.

### 14.7.1 Factors that may alter the choice of prophylaxis

Factors that might alter the risk of VTE

• Severe Head Injury, Spinal injury associated with altered conscious level and/or limb paralysis, increase the risk of VTE because early ambulation is not possible and a prolonged period of recumbency is inevitable. There is, however, no particular contraindication to any of the methods of prophylaxis for these patients.

• An increased risk of VTE is associated with Brain (malignant or benign) tumours and Cerebral Haemorrhage (Stroke.

Factors that increase the risk of bleeding or the hazard associated with it

• The risk of bleeding is a serious complication in patients requiring emergency neurosurgery.

• The timing of when pharmacological prophylaxis is started is particularly important because of the risk from bleeding.

Other factors that would affect the choice of, and use of, prophylaxis:

• Many neurosurgical patients are on high doses of glucocorticoids which may alter the coagulation status of the patient.

• Some patients undergoing prolonged cranial surgery e.g Meningiomas are at risk of developing disseminated intravascular coagulation

### 14.7.2 Evidence

There is little RCT evidence directly related to neurosurgery or spinal surgery. The data for all RCTs were sub-grouped to determine if there was a difference between surgical specialities and the effectiveness of each method of prophylaxis. We did not find reliable statistical evidence to be certain of a difference. Consequently, to get a reliable estimate of effectiveness of different prophylaxis we analysed the RCTs for all surgical specialities together. The risk for developing a DVT varies depending on the baseline risk for each type of surgery and the patient specific risk factors.

We have estimated, from the incidence in the RCTs (Chapter 4), that the risk of developing deep vein thrombosis in neurosurgery patients not receiving thromboprophylaxis is 20% (95%CI: 17% to 24%). Our model suggests that a mechanical method of prophylaxis (i.e. graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices) is cost effective in all patients undergoing neurosurgery. Mechanical prophylaxis

plus low molecular weight heparin is cost effective in patients at increased risk of venous thromboembolism. Fondaparinux in not licensed for use with these patients.

The GDG recognised that patients with ruptured cranial or spinal vascular malformations (e.g. brain aneurysms) may be at risk of neurological damage and pharmacological prophylaxis prior to the definitive treatment of the lesion needs to be avoided.

### 14.7.3 Neurosurgery recommendations

**Patients having neurosurgery should be offered mechanical prophylaxis.**

**Patients having neurosurgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LMWH.**

**Patients with ruptured cranial or spinal vascular malformations (e.g. brain aneurysms) should not be offered pharmacological prophylaxis until the lesion has been secured.**

## 14.8 *Vascular surgery*

This section covers inpatients undergoing vascular surgery. Vascular surgery encompasses two distinct patient populations: surgery for peripheral arterial disease (PAD) including carotid, aorto-iliac and limb arterial surgery; and patients with venous disease (superficial or deep venous reflux and varicose veins). A significant proportion of surgery for uncomplicated primary varicose veins is undertaken as day case procedures, these patients would not therefore be covered by these recommendations.

### 14.8.1 Factors that may alter the choice of prophylaxis

Factors that might alter the risk of VTE

- Arterial surgery patients are often elderly and immobile.

- Many arterial surgery patients will already be receiving antiplatelet therapy and a small proportion will be on warfarin.

- Systemic heparin is frequently administered during surgery for arterial disease.

- Surgery for varicose veins is mostly in women, oral contraceptive use and hormone replacement therapy are therefore more commonly associated with varicose veins surgery.

Factors that increase the risk of bleeding or the hazard associated with it

- Patients using anticoagulation or antiplatelet therapy not related to surgery will have an increased risk of bleeding.

Other factors that may alter the choice of prophylaxis

- The use of intermittent compression devices and compression stockings will usually be inappropriate on the operated leg for a patient undergoing lower limb arterial surgery.

- Graduated compression stockings will be contraindicated for patients with lower limb arterial disease.

### 14.8.2 Evidence

There is little RCT evidence directly related to vascular surgery. The data for all RCTs were sub-grouped to determine if there was a difference by surgical speciality. We did not find reliable statistical evidence to be certain of a difference between surgical specialities in the effectiveness of any method of prophylaxis. Consequently, to get a reliable estimate of effectiveness of different prophylaxis we analysed the RCTs for all surgical specialities together. The risk for developing a DVT varies depending on the baseline risk for each type of surgery and the patient specific risk factors.

We did not have enough data, from the incidence in the RCTs (Chapter 4), to enable us to estimate the risk of developing deep vein thrombosis in vascular surgery patients not receiving thromboprophylaxis, according to our HES data, its ranking in among amongst other surgeries would suggest that the risk is relatively high. Our model suggests that a mechanical method of prophylaxis (i.e. graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices) is cost effective even in patients at moderate risk. We believe that a mechanical method of prophylaxis plus low molecular weight heparin is likely to be cost effective in patients at increased risk of venous thromboembolism. Fondaparinux in not licensed for use with these patients.

### 14.8.3 Recommendations

**Patients having vascular surgery should be offered mechanical prophylaxis.**

**Patients having vascular surgery with one or more risk factors for VTE (see box 1) should be offered mechanical prophylaxis and LMWH.**

# 15 Bibliography


1. Small doses of subcutaneous sodium heparin in the prevention of deep vein thrombosis after elective hip operations. *British Journal of Surgery* 1975, **62**(5):348-50. *(Guideline Ref ID: ANON1975)*

2. Cost Effectiveness Analysis Registry http://www.tufts-nemc.org/cearegistry/ [accessed 1-7-2006]. *(Guideline Ref ID: CEA2006)*

3. Abdool-Carrim T., Adler H, Becker P, Carides M, Ginsberg J, Golele R *et al*. The cost and benefit of prophylaxis against deep vein thrombosis in elective hip replacement. DVT/PE Prophylaxis Consensus Forum. *South African Medical Journal* 1997, **87**(5):594-600. *(Guideline Ref ID: ABDOOL1997)*

4. Abernethy EA, Hartsuck JM. Postoperative pulmonary embolism. A prospective study utilizing low dose heparin. *American Journal of Surgery* 1974, **128**(6):739-42. *(Guideline Ref ID: ABERNETHY1974)*

5. Abraham-Inpijn L. Critical evaluation of low-dose heparin in laryngectomy. *Archivum Chirurgicum Neerlandicum* 1979, **31**(1):9-15. *(Guideline Ref ID: ABRAHAM1979)*

6. Abraham-Inpijn L, Vreeken J. Effect of low-dose heparin on incidence of postoperative thrombosis in orthopaedic patients. *Archivum Chirurgicum Neerlandicum* 1975, **27**(1):63-8. *(Guideline Ref ID: ABRAHAM1975)*

7. Adolf J, Fritsche HM, Haas S, Hennig FF, Horbach T, Kastl S *et al*. Comparison of 3,000 IU aXa of the low molecular weight heparin certoparin with 5,000 IU aXa in prevention of deep vein thrombosis after total hip replacement. German Thrombosis Study Group. *International Angiology* 1999, **18**(2):122-6. *(Guideline Ref ID: ADOLF1999)*

8. Adolf J, Knee H, Roder JD, van de FE, Siewert JR. [Thromboembolism prophylaxis with low molecular weight heparin in abdominal surgery]. *Deutsche Medizinische Wochenschrift* 1989, **114**(2):48-53. *(Guideline Ref ID: ADOLF1989)*

9. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *British Journal of Surgery* 2005, **92**(10):1212-20. *(Guideline Ref ID: AGNELLI2005)*

10. Agnelli G, Piovella F, Buoncristiani P, Severi P, Pini M, D'Angelo A *et al*. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *New England Journal of Medicine* 1998, **339**(2):80-5. *(Guideline Ref ID: AGNELLI1998)*

11. Alfaro MJ, Paramo JA, Rocha E. Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. *Thrombosis and Haemostasis* 1986, **56**(1):53-6. *(Guideline Ref ID: ALFARO1986)*

12. Alho A, Stangeland L, Røttingen J, Wiig JN. Prophylaxis of venous thromboembolism by aspirin, warfarin and heparin in patients with hip fracture. A prospective clinical study with cost-benefit analysis. *Annales Chirurgiae et Gynaecologiae* 1984, **73**(4):225-8. *(Guideline Ref ID: ALHO1984)*

13. Allan A, Williams JT, Bolton JP, Le Quesne LP. The use of graduated compression stockings in the prevention of postoperative deep vein thrombosis. *British Journal of Surgery* 1983, **70**(3):172-4. *(Guideline Ref ID: ALLAN1983)*

14. Allen NH, Jenkins JD, Smart CJ. Surgical haemorrhage in patients given subcutaneous heparin as prophylaxis against thromboembolism. *British Medical Journal* 1978, **1**(6123):1326. *(Guideline Ref ID: ALLEN1978)*

15. Amaragiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. *Cochrane Database of Systematic Reviews* 2000, **Issue 1**:CD001484. *(Guideline Ref ID: AMARAGIRI2000)*

16. Anderson DR, O'Brien BJ, Levine MN, Roberts R, Wells PS, Hirsh J. Efficacy and cost of low-

molecular-weight heparin compared with standard heparin for the prevention of deep vein thrombosis after total hip arthroplasty. *Annals of Internal Medicine* 1993, **119**(11):1105-12. *(Guideline Ref ID: ANDERSON1993)*

17. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003, **107**(23 Suppl 1):I-9-I-16. *(Guideline Ref ID: ANDERSON2003)*

18. Anderson P, Kjaersgaard E, Beyer-Hogersen R, Fredericksen E. DHEH and dextran 70 in thromboprophylaxis after hip fracture. *Acta Orthopaedica Scandinavica* 1986, **57**:469. *(Guideline Ref ID: ANDERSON1986)*

19. Andtbacka RH, Babiera G, Singletary SE, Hunt KK, Meric-Bernstam F, Feig BW *et al*. Incidence and prevention of venous thromboembolism in patients undergoing breast cancer surgery and treated according to clinical pathways. *Annals of Surgery* 2006, **243**(1):96-101. *(Guideline Ref ID: ANDTBACKA2006)*

20. Anglen JO, Bagby C, George R. A randomized comparison of sequential-gradient calf compression with intermittent plantar compression for prevention of venous thrombosis in orthopedic trauma patients: preliminary results. *American Journal of Orthopedics* 1998, **27**(1):53-8. *(Guideline Ref ID: ANGLEN1998)*

21. Annemans L, Minjoulat-Rey MC, De Knock M, Vranckx K, Czarka M, Gabriel S *et al*. Cost consequence analysis of fondaparinux versus enoxaparin in the prevention of venous thromboembolism after major orthopaedic surgery in Belgium. *Acta Clinica Belgica* 2004, **59**(6):346-57. *(Guideline Ref ID: ANNEMANS2004)*

22. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994, **308**(6923):235-46. *(Guideline Ref ID: ANTIPLATELET1994)*

23. Aryal KR, Al Khaffaf H. Venous thromboembolic complications following air travel: what's the quantitative risk? A literature review. *European Journal of Vascular and Endovascular Surgery* 2006, **31**(2):187-99. *(Guideline Ref ID: ARYAL2006)*

24. Auguste KI, Quinones-Hinojosa A, Gadkary C, Zada G, Lamborn KR, Berger MS. Incidence of venous thromboembolism in patients undergoing craniotomy and motor mapping for glioma without intraoperative mechanical prophylaxis to the contralateral leg. *Journal of Neurosurgery* 2003, **99**(4):680-4. *(Guideline Ref ID: AUGUSTE2003)*

25. Avikainen V, von Bonsdorff H, Partio E, Kaira P, Hakkinen S, Usenius JP *et al*. Low molecular weight heparin (enoxaparin) compared with unfractionated heparin in prophylaxis of deep venous thrombosis and pulmonary embolism in patients undergoing hip replacement. *Annales Chirurgiae et Gynaecologiae* 1995, **84**(1):85-90. *(Guideline Ref ID: AVIKAINEN1995)*

26. Bachmann F, McKenna R, Meredith P, Carta S. [Intermittent pneumatic compression of leg and thigh: a new successful method for the prevention of postoperative thrombosis]. *Schweizerische Medizinische Wochenschrift* 1976, **106**(50):1819-21. *(Guideline Ref ID: BACHMANN1976)*

27. Bailey JP, Kruger MP, Solano FX, Zajko AB, Rubash HE. Prospective randomized trial of sequential compression devices vs low-dose warfarin for deep venous thrombosis prophylaxis in total hip arthroplasty. *Journal of Arthroplasty* 1991, **6 Suppl**:S29-S35. *(Guideline Ref ID: BAILEY1991)*

28. Balas PE. Efficiacy and safety of nadroparin (Fraxiparine) versus placebo in the prophylactic treatment of deep vein thrombosis in patients with high thrombo-embolic risk undergoing general surgery. *Thrombosis Research* 1992, **65 Suppl 1**:S113. *(Guideline Ref ID: BALAS1992)*

29. Ballard RM, Bradley-Watson PJ, Johnstone FD, Kenney A, McCarthy TG. Low doses of subcutaneous heparin in the prevention of deep vein thrombosis after gynaecological surgery. *Journal of Obstetrics & Gynaecology of the British Commonwealth* 1973, **80**(5):469-72. *(Guideline Ref ID: BALLARD1973)*

30. Barber HM, Feil EJ, Galasko CS, Edwards DH, Sutton RA, Haynes DW *et al*. A comparative study of dextran-70, warfarin and low-dose heparin for the prophylaxis of thrombo-embolism following total hip replacement. *Postgraduate Medical Journal* 1977, **53**(617):130-3. *(Guideline Ref ID: BARBER1977)*

31. Barbui T, Cassinelli G, Cortelazzo S, D'Alonzo U, Fantoni P, Lavorato F. Comparison of low molecular weight heparin CY 216 and unfractionated heparin in preventing post-operative venous thromboembolism in general surgery: a preliminary results of a cooperative

study. *Fibrinolysis* 1990, **4 Suppl 1**:79. *(Guideline Ref ID: BARBUI1990)*

32. Barker SGE, Hollingsworth SJ. Wearing graduated compression stockings: The reality of everyday deep vein thrombosis prophylaxis. *Phlebology* 2004, **19**(1):52-3. *(Guideline Ref ID: BARKER2004)*

33. Barnes RW, Brand RA, Clarke W, Hartley N, Hoak JC. Efficacy of graded-compression antiembolism stockings in patients undergoing total hip arthroplasty. *Clinical Orthopaedics and Related Research* 1978,(132):61-7. *(Guideline Ref ID: BARNES1978)*

34. Bates D, DebRoy S, Sarkar D. nlme: Linear and nonlinear mixed effects models. R package version 3.1-66. 2005. *(Guideline Reference ID: PINHEIRO2005)*

35. Bauer KA, Eriksson B, I, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *New England Journal of Medicine* 2001, **345**(18):1305-10. *(Guideline Ref ID: BAUER2001)*

36. Baumgartner A, Jacot N, Moser G, Krahenbuhl B. Prevention of postoperative deep vein thrombosis by one daily injection of low molecular weight heparin and dihydroergotamine. *Vasa* 1989, **18**(2):152-6. *(Guideline Ref ID: BAUMGARTNER1989)*

37. Beck JR, Pauker SG. The Markov process in medical prognosis. *Medical Decision Making* 1983, **3**(4):419-58. *(Guideline Ref ID: BECK1983)*

38. Beghi C, Fragnito C, Antonelli A, Reverberi C, Ferrari P, Saccani S *et al*. Prevention of deep venous thrombosis by a new low molecular weight heparin (Fluxum) in cardiac surgery. *International Angiology* 1993, **12**(4):383-6. *(Guideline Ref ID: BEGHI1993)*

39. Beisaw NE, Comerota AJ, Groth HE, Merli GJ, Weitz HH, Zimmerman RC *et al*. Dihydroergotamine/heparin in the prevention of deep-vein thrombosis after total hip replacement. A controlled, prospective, randomized multicenter trial. *Journal of Bone and Joint Surgery* 1988, **70**(1):2-10. *(Guideline Ref ID: BEISAW1988)*

40. Bejjani BB, Chen DC, Nolan NG, Edson M. Minidose heparin in transurethral prostatectomy. *Urology* 1983, **22**(3):251-4. *(Guideline Ref ID: BEJJANI1983)*

41. Belch JJ, Lowe GD, Pollock JG, Forbes CD, Prentice CR. Low dose heparin in the prevention of deep-vein thrombosis after aortic bifurcation graft surgery. *Thrombosis and Haemostasis* 1980, **42**(5):1429-33. *(Guideline Ref ID: BELCH1980)*

42. Benkö T, Cooke EA, McNally MA, Mollan RA. Graduated compression stockings: knee length or thigh length. *Clinical Orthopaedics and Related Research* 2001,(383):197-203. *(Guideline Ref ID: BENKO2001)*

43. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A *et al*. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *New England Journal of Medicine* 2002, **346**(13):975-80. *(Guideline Ref ID: BERGQVIST2002D)*

44. Bergqvist D, Benoni G, Björgell O, Fredin H, Hedlundh U, Nicolas S *et al*. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *The New England Journal of Medicine* 1996, **335**(10):696-700. *(Guideline Ref ID: BERGQVIST1996B)*

45. Bergqvist D, Breddin K, ten Cate JW, Davidson JF, Haas S, Leyvraz PF *et al*. Thromboprophylaxis in hip fracture surgery: A pilot study comparing danaparoid, enoxaparin and dalteparin. *Haemostasis* 1999, **29**(6):310-7. *(Guideline Ref ID: BERGQVIST1999A)*

46. Bergqvist D, Burmark US, Flordal PA, Frisell J, Hallböök T, Hedberg M *et al*. Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2500 versus 5000 Xal units in 2070 patients. *British Journal of Surgery* 1995, **82**(4):496-501. *(Guideline Ref ID: BERGQVIST1995)*

47. Bergqvist D, Burmark US, Frisell J, Guilbaud O, Hallbook T, Horn A *et al*. Thromboprophylactic effect of low molecular weight heparin started in the evening before elective general abdominal surgery: a comparison with low-dose heparin. *Seminars in Thrombosis and Hemostasis* 1990, **16 Suppl**:19-24. *(Guideline Ref ID: BERGQVIST1990A)*

48. Bergqvist D, Burmark US, Frisell J, Hallbook T, Lindblad B, Risberg B *et al*. Low molecular weight heparin once daily compared with conventional low-dose heparin twice daily. A prospective double-blind multicentre trial on prevention of postoperative thrombosis. *British Journal of Surgery* 1986, **73**(3):204-8. *(Guideline Ref ID: BERGQVIST1986A)*

49. Bergqvist D, Efsing HO, Hallbook T, Hedlund T. Thromboembolism after elective and post-traumatic hip surgery--a controlled

prophylactic trial with dextran 70 and low-dose heparin. *Acta Chirurgica Scandinavica* 1979, **145**(4):213-8. *(Guideline Ref ID: BERGQVIST1979)*

50. Bergqvist D, Eldor A, Thorlacius-Ussing O, Combe S, Cossec-Vion MJ. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: A double-blind randomized multicentre trial with venographic assessment. *British Journal of Surgery* 1997, **84**(8):1099-103. *(Guideline Ref ID: BERGQVIST1997B)*

51. Bergqvist D, Flordal PA, Friberg B, Frisell J, Hedberg M, Ljungström KG *et al*. Thromboprophylaxis with a low molecular weight heparin (tinzaparin) in emergency abdominal surgery. A double-blind multicenter trial. *Vasa* 1996, **25**(2):156-60. *(Guideline Ref ID: BERGQVIST1996F)*

52. Bergqvist D, Hallbook T. Prophylaxis of postoperative venous thrombosis in a controlled trial comparing dextran 70 and low-dose heparin. *World Journal of Surgery* 1980, **4**(2):239-43. *(Guideline Ref ID: BERGQVIST1980)*

53. Bergqvist D, Jendteg S, Johansen L, Persson U, Odegaard K. Cost of long-term complications of deep venous thrombosis of the lower extremities: an analysis of a defined patient population in Sweden. *Annals of Internal Medicine* 1997, **126**:454-7. *(Guideline Ref ID: BERGQVIST1997)*

54. Bergqvist D, Jonsson B. Cost-effectiveness of prolonged administration of a low molecular weight herapin for the prevention of deep venous thrombosis following total hip replacement. *Value in Health* 1999, **2**(4):288-94. *(Guideline Ref ID: BERGQVIST1999)*

55. Bergqvist D, Kettunen K, Fredin H, Fauno P, Suomalainen O, Soimakallio S *et al*. Thromboprophylaxis in patients with hip fractures: a prospective, randomized, comparative study between Org 10172 and dextran 70. *Surgery* 1991, **109**(5):617-22. *(Guideline Ref ID: BERGQVIST1991)*

56. Bergqvist D, Lindblad B. The thromboprophylactic effect of graded elastic compression stockings in combination with dextran 70. *Archives of Surgery* 1984, **119**(11):1329-31. *(Guideline Ref ID: BERGQVIST1984)*

57. Bergqvist D, Matzsch T. Cost/benefit aspects on thromboprophylaxis. *Haemostasis* 1993, **23**(Suppl 1):15-9. *(Guideline Ref ID: BERGQVIST1993)*

58. Bergqvist D, Matzsch T, Burmark US, Frisell J, Guilbaud O, Hallbook T *et al*. Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. *British Journal of Surgery* 1988, **75**(9):888-91. *(Guideline Ref ID: BERGQVIST1988A)*

59. Bern MM, Bierbaum B, Wetzner S, Brennan W, McAlister S. Very low dose warfarin as prophylaxis against ultrasound detected deep vein thrombosis following primary hip replacement. *American Journal of Hematology* 2002, **71**(2):69-74. *(Guideline Ref ID: BERN2002)*

60. Bhatia RS, Collingwood P, Bartlett P. Radiologic versus surgical placement of vena cava filters: a comparative study of cost, time and complications. *Canadian Association of Radiologists Journal* 1998, **49**(2):79-83. *(Guideline Ref ID: BHATIA1998)*

61. Biegholdt M. Descriptive analysis of the European Fraxiparin Study. *Seminars in Thrombosis and Hemostasis* 1989, **15**(4):409-13. *(Guideline Ref ID: BIEGHOLDT1989)*

62. Bischof M, Leuppi JD, Sendi P. Cost-effectiveness of extended venous thromboembolism prophylaxis with fondaparinux in hip surgery patients. *Expert Review of Pharmacoeconomics and Outcomes Research* 2006, **6**(2):171-80. *(Guideline Ref ID: BISCHOF2006)*

63. Bjornara BT, Gudmundsen TE, Dahl OE. Frequency and timing of clinical venous thromboembolism after major joint surgery. *Journal of Bone and Joint Surgery British Volume* 2006, **88**(3):386-91. *(Guideline Ref ID: BJORNARA2006)*

64. Bjorvatn A, Kristiansen F. Fondaparinux sodium compared with enoxaparin sodium: A cost-effectiveness analysis. *American Journal of Cardiovascular Drugs* 2005, **5**(2):121-30. *(Guideline Ref ID: BJORVATN2005)*

65. Blackshear WM, Jr., Prescott C, LePain F, Benoit S, Dickstein R, Seifert KB. Influence of sequential pneumatic compression on postoperative venous function. *Journal of Vascular Surgery* 1987, **5**(3):432-6. *(Guideline Ref ID: BLACKSHEAR1987)*

66. Blanchard J, Meuwly JY, Leyvraz PF, Miron MJ, Bounameaux H, Hoffmeyer P *et al*. Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between

a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. *Journal of Bone and Joint Surgery British Volume* 1999, **81**(4):654-9. *(Guideline Ref ID: BLANCHARD1999A)*

67. Boehringer Ingelheim. (1976) DVT nach Hirntumoroperationen. Bracknell: Boehringer Ingelheim. *(Guideline Ref ID: BOEHRINGER1976)*

68. Boneu B. An international multicentre study: Clivarin in the prevention of venous thromboembolism in patients undergoing general surgery. Report of the International Clivarin Assessment Group. *Blood Coagulation and Fibrinolysis* 1993, **4 Suppl 1**:S21-S22. *(Guideline Ref ID: BONEU1993)*

69. Bonnar J, Walsh J. Prevention of thrombosis after pelvic surgery by British dextran 70. *The Lancet* 1972, **1**(7751):614-6. *(Guideline Ref ID: BONNAR1972)*

70. Borgstrom S, Greitz T, Van der Linden W, Molin J, Rudics I. Anticoagulation prophylaxis of venous thrombosis in patients with fractured neck of the femur. *Acta Chirurgica Scandinavica* 1965, **129**:500-8. *(Guideline Ref ID: BORGSTROM1965)*

71. Borris LC, Hauch O, Jorgensen LN, Lassen MR, Wille-Jorgensen P, Sorensen JV *et al*. Low-molecular-weight heparin (enoxaparin) vs dextran 70: The prevention of postoperative deep vein thrombosis after total hip replacement. *Archives of Internal Medicine* 1991, **151**(8):1621-4. *(Guideline Ref ID: BORRIS1991A)*

72. Borris LC, Lassen MR, Jensen HP, Andersen BS, Poulsen KA. Perioperative thrombosis prophylaxis with low molecular weight heparins in elective hip surgery: clinical and economic considerations. *International Journal of Clinical Pharmacology and Therapeutics* 1994, **32**(5):262-8. *(Guideline Ref ID: BORRIS1994)*

73. Borstad E, Urdal K, Handeland G, Abildgaard U. Comparison of low molecular weight heparin vs. unfractionated heparin in gynecological surgery. *Acta Obstetricia et Gynecologica Scandinavica* 1988, **67**(2):99-103. *(Guideline Ref ID: BORSTAD1988)*

74. Borstad E, Urdal K, Handeland G, Abildgaard U. Comparison of low molecular weight heparin vs. unfractionated heparin in gynecological surgery. II: Reduced dose of low molecular weight heparin. *Acta Obstetricia et Gynecologica Scandinavica* 1992, **71**(6):471-5. *(Guideline Ref ID: BORSTAD1992)*

75. Botteman MF, Caprini J, Stephens JM, Nadipelli V, Bell CF, Pashos CL *et al*. Results of an economic model to assess the cost-effectiveness of enoxaparin, a low-molecular-weight heparin, versus warfarin for the prophylaxis of deep vein thrombosis and associated long-term complications in total hip replacement surgery in the United States. *Clinical Therapeutics* 2002, **24**(11):1960-86. *(Guideline Ref ID: BOTTEMAN2002)*

76. Braithwaite RS, Chlebowski RT, Lau J, George S, Hess R, Col NF. Meta-analysis of vascular and neoplastic events associated with tamoxifen. *Journal of General Internal Medicine* 2003, **18**(11):937-47. *(Guideline Ref ID: BRAITHWAITE2003)*

77. Brasel KJ, Borgstrom DC, Weigelt JA. Cost-effective prevention of pulmonary embolus in high-risk trauma patients. *Journal of Trauma* 1997, **42**(3):456-60. *(Guideline Ref ID: BRASEL1997)*

78. Brichant JF, Blom-Peters L, Buffels R, Lamy M. Central neural blockade failed to decrease deep venous thrombosis in patients undergoing hip surgery and receiving low molecular weight heparin. *British Journal of Anaesthesia* 1995, **74**(Suppl. 1):75. *(Guideline Ref ID: BRICHANT1995)*

79. Briel RC, Doller P, Hermann CP. [Prevention of thromboembolism in hysterectomies with low molecular weight heparin Fragmin]. *Geburtshilfe Frauenheilkd* 1988, **48**(3):160-4. *(Guideline Ref ID: BRIEL1988)*

80. British Committee for Standards in Haematology. Guidelines on use of Vena Cava Filters http://www.bcshguidelines.com/pdf/intirumIVCfilterguidelines.pdf [accessed 31-5-0006]. *(Guideline Ref ID: BCSH2006)*

81. British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax* 2003, **58**(6):470-83. *(Guideline Ref ID: BTS2003)*

82. Broadman LM. Non-steroidal anti-inflammatory drugs, antiplatelet medications and spinal axis anesthesia. *Best Practice & Research Clinical Anaesthesiology* 2005, **19**(1):47-58. *(Guideline Ref ID: BROADMAN2005)*

83. Browse NL, Negus D. Prevention of postoperative leg vein thrombosis by electrical muscle stimulation. An evaluation with 125I-labelled fibrinogen. *British Medical Journal*

1970, **3**(723):615-8. *(Guideline Ref ID: BROWSE1970A)*

84. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology* 1997, **50**(6):683-91. *(Guideline Ref ID: BUCHER1997)*

85. Burns PJ, Wilsom RG, Cunningham C. Venous thromboembolism prophylaxis used by consultant general surgeons in Scotland. *Journal of the Royal College of Surgeons of Edinburgh* 2001, **46**(6):329-33. *(Guideline Ref ID: BURNS2001)*

86. Butson AR. Intermittent pneumatic calf compression for prevention of deep venous thrombosis in general abdominal surgery. *American Journal of Surgery* 1981, **142**(4):525-7. *(Guideline Ref ID: BUTSON1981)*

87. Bynke O, Hillman J, Lassvik C. Does peroperative external pneumatic leg muscle compression prevent post-operative venous thrombosis in neurosurgery? *Acta Neurochirurgica* 1987, **88**(1-2):46-8. *(Guideline Ref ID: BYNKE1987)*

88. Cade JF, Clegg EA, Westlake GW. Prophylaxis of venous thrombosis after major thoracic surgery. *Australian and New Zealand Journal of Surgery* 1983, **53**(4):301-4. *(Guideline Ref ID: CADE1983)*

89. Caen JP. A randomized double-blind study between a low molecular weight heparin Kabi 2165 and standard heparin in the prevention of deep vein thrombosis in general surgery. A French multicenter trial. *Thrombosis and Haemostasis* 1988, **59**(2):216-20. *(Guideline Ref ID: CAEN1988)*

90. Caloghera C, Bordos D, Miculit F, Aboubakr W, Teodorescu C, Vancea D. (Prevention of postoperative thromboembolism with small doses of heparin). *Revista de Chirurgie, Oncologie, Radiologie, O R L , Oftalmologie, Stomatologie Chirurgie* 1984, **33**(3):161-7. *(Guideline Ref ID: CALOGHERA1984)*

91. Caprini JA, Arcelus J, I, Kudrna JC, Sehgal LR, Oyslender M, Maksimovic D *et al*. Cost-effectiveness of venous thromboembolism prophylaxis after total hip replacement. *Phlebology* 2002, **17**(3-4):126-33. *(Guideline Ref ID: CAPRINI2002A)*

92. Caprini JA, Chucker JL, Zuckerman L. Thrombosis prophylaxis using external compression. *Surgery, Gynecology & Obstetrics* 1983, **156**(5):599-604. *(Guideline Ref ID: CAPRINI1983)*

93. Carter AE, Eban R. The prevention of postoperative deep venous thrombosis with dextran 70. *British Journal of Surgery* 1973, **60**(9):681-3. *(Guideline Ref ID: CARTER1973)*

94. Catania G, Salanitri G. Prevention of postoperative deep vein thrombosis by two different heparin types. *International Journal of Clinical Pharmacology, Therapy and Toxicology* 1988, **26**(6):304-9. *(Guideline Ref ID: CATANIA1988)*

95. Cerrato D, Ariano C, Fiacchino F. Deep vein thrombosis and low-dose heparin prophylaxis in neurosurgical patients. *Journal of Neurosurgery* 1978, **49**(3):378-81. *(Guideline Ref ID: CERRATO1978)*

96. Chandhoke PS, Gooding GA, Narayan P. Prospective randomized trial of warfarin and intermittent pneumatic leg compression as prophylaxis for postoperative deep venous thrombosis in major urological surgery. *Journal of Urology* 1992, **147**(4):1056-9. *(Guideline Ref ID: CHANDHOKE1992)*

97. Chau Q, Cantor SB, Caramel E, Hicks M, Kurtin D, Grover T *et al*. Cost-effectiveness of the bird's nest filter for preventing pulmonary embolism among patients with malignant brain tumors and deep venous thrombosis of the lower extremities. *Supportive Care in Cancer* 2003, **11**(12):795-9. *(Guideline Ref ID: CHAU2003)*

98. Choudhry NK, Anderson GM, Laupacis A, Ross-Degnan D, Normand SL, Soumerai SB. Impact of adverse events on prescribing warfarin in patients with atrial fibrillation: matched pair analysis. *BMJ* 2006, **332**(7534):141-5. *(Guideline Ref ID: CHOUDHRY2006)*

99. Christensen SW, Wille-Jørgensen P, Bjerg-Nielsen A, Kjaer L. Prevention of deep venous thrombosis following total hip replacement, using epidural analgesia. *Acta Orthopaedica Belgica* 1989, **55**(1):58-61. *(Guideline Ref ID: CHRISTENSEN1989A)*

100. Clagett GP, Schneider P, Rosoff CB, Salzman EW. The influence of aspirin on postoperative platelet kinetics and venous thrombosis. *Surgery* 1975, **77**(1):61-74. *(Guideline Ref ID: CLAGETT1975)*

101. Clark WB, MacGregor AB, Prescott RJ, Ruckley CV. Pneumatic compression of the calf and postoperative deep-vein thrombosis. *The Lancet* 1974, **2**(7871):5-7. *(Guideline Ref ID: CLARK1974)*

102. Clarke-Pearson DL, Coleman RE, Synan IS, Hinshaw W, Creasman WT. Venous thromboembolism prophylaxis in gynecologic oncology: a prospective, controlled trial of low-dose heparin. *American Journal of Obstetrics and Gynecology* 1983, **145**(5):606-13. *(Guideline Ref ID: CLARKEPEARSON1983)*

103. Clarke-Pearson DL, Creasman WT, Coleman RE, Synan IS, Hinshaw WM. Perioperative external pneumatic calf compression as thromboembolism prophylaxis in gynecologic oncology: report of a randomized controlled trial. *Gynecologic Oncology* 1984, **18**(2):226-32. *(Guideline Ref ID: CLARKEPEARSON1984B)*

104. Clarke-Pearson DL, DeLong E, Synan IS, Soper JT, Creasman WT, Coleman RE. A controlled trial of two low-dose heparin regimens for the prevention of postoperative deep vein thrombosis. *Obstetrics and Gynecology* 1990, **75**(4):684-9. *(Guideline Ref ID: CLARKEPEARSON1990)*

105. Clarke-Pearson DL, Synan IS, Dodge R, Soper JT, Berchuck A, Coleman RE. A randomized trial of low-dose heparin and intermittent pneumatic calf compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. *American Journal of Obstetrics and Gynecology* 1993, **168**(4):1146-53. *(Guideline Ref ID: CLARKEPEARSON1993)*

106. Clarke-Pearson DL, Synan IS, Hinshaw WM, Coleman RE, Creasman WT. Prevention of postoperative venous thromboembolism by external pneumatic calf compression in patients with gynecologic malignancy. *Obstetrics and Gynecology* 1984, **63**(1):92-8. *(Guideline Ref ID: CLARKEPEARSON1984A)*

107. Coe NP, Collins RE, Klein LA, Bettmann MA, Skillman JJ, Shapiro RM *et al*. Prevention of deep vein thrombosis in urological patients: a controlled, randomized trial of low-dose heparin and external pneumatic compression boots. *Surgery* 1978, **83**(2):230-4. *(Guideline Ref ID: COE1978)*

108. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *New England Journal of Medicine* 1988, **318**(18):1162-73. *(Guideline Ref ID: COLLINS1988)*

109. Colwell CW, Jr., Collis DK, Paulson R, McCutchen JW, Bigler GT, Lutz S *et al*. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three months after discharge. *Journal of Bone and Joint Surgery American Volume* 1999, **81**(7):932-40. *(Guideline Ref ID: COLWELL1999)*

110. Colwell CW, Jr., Pulido P, Hardwick ME, Morris BA. Patient compliance with outpatient prophylaxis: An observational study. *Orthopedics* 2005, **28**(2):143-7. *(Guideline Ref ID: COLWELL2005)*

111. Colwell CW, Jr., Spiro TE. Efficacy and safety of enoxaparin to prevent deep vein thrombosis after hip arthroplasty. *Clinical Orthopaedics and Related Research* 1995,(319):215-22. *(Guideline Ref ID: COLWELL1995A)*

112. Colwell CW, Jr., Spiro TE, Trowbridge AA, Morris BA, Kwaan HC, Blaha JD *et al*. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group. *Journal of Bone and Joint Surgery* 1994, **76**(1):3-14. *(Guideline Ref ID: COLWELL1994A)*

113. Colwell CW, Spiro TE, Trowbridge AA, Stephens JW, Gardiner GA, Ritter MA. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep venous thrombosis after elective knee arthroplasty. Enoxaparin Clinical Trial Group. *Clinical Orthopaedics and Related Research* 1995,(321):19-27. *(Guideline Ref ID: COLWELL1995D)*

114. Combe S, Samama MM. Prevention of thromboembolic disease in general surgery with clexane (enoxaparin). *Seminars in Thrombosis and Hemostasis* 1991, **17 Suppl 3**:291-5. *(Guideline Ref ID: COMBE1991)*

115. Comp PC, Spiro TE, Friedman RJ, Whitsett TL, Johnson GJ, Gardiner GA, Jr. *et al*. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. *Journal of Bone and Joint Surgery American Volume* 2001, **83**(3):336-45. *(Guideline Ref ID: COMP2001)*

116. Comp PC, Voegeli T, McCutchen JW, Skoutakis VA, Trowbridge A, Overdyke WL. A comparison of danaparoid and warfarin for prophylaxis against deep vein thrombosis after total hip replacement: The Danaparoid Hip Arthroplasty Investigators Group. *Orthopedics* 1998, **21**(10):1123-8. *(Guideline Ref ID: COMP1998)*

117. Covey TH, Sherman L, Baue AE. Low-dose heparin in postoperative patients: a prospective, coded study. *Archives of Surgery* 1975, **110**(8):1021-6. *(Guideline Ref ID: COVEY1975)*

118. Creperio G, Marabini M, Ciocia G, Bergonzi M, Fincato M. (Evaluation of the effectiveness and safety of Fragmin (Kabi 2165) versus calcium heparin in the prevention of deep venous thrombosis in general surgery). *Minerva Chirurgica* 1990, **45**(17):1101-6. *(Guideline Ref ID: CREPERIO1990)*

119. Curtis L, Netten A. (2005) Unit costs of health and social care 2005. Canterbury: Personal Social Services Research Unit, University of Kent. *(Guideline Ref ID: CURTIS2005)*

120. Dahan M, Levasseur P, Boqaty J, Boneu B, Samama M. Prevention of post-operative deep vein thrombosis (DVT) in malignant patients by fraxiparine (a low molecular weight heparin). A co-operative trial. *Thrombosis & Haemostasis* 1989, **62**(1):519. *(Guideline Ref ID: DAHAN1989)*

121. Dahl OE, Andreassen G, Aspelin T, Müller C, Mathiesen P, Nyhus S *et al*. Prolonged thromboprophylaxis following hip replacement surgery -- results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). *Thrombosis and Haemostasis* 1997, **77**(1):26-31. *(Guideline Ref ID: DAHL1997)*

122. Dahl OE, Pleil AM. Investment in prolonged thromboprophylaxis with dalteparin improves clinical outcomes after hip replacement. *Journal of Thrombosis and Haemostasis : JTH* 2003, **1**(5):896-906. *(Guideline Ref ID: DAHL2003)*

123. Dainty L, Maxwell GL, Clarke-Pearson DL, Myers ER. Cost-effectiveness of combination thromboembolism prophylaxis in gynecologic oncology surgery. *Gynecologic Oncology* 2004, **93**(2):366-73. *(Guideline Ref ID: DAINTY2004)*

124. Dauphin A, Raymer KE, Stanton EB, Fuller HD. Comparison of general anesthesia with and without lumbar epidural for total hip arthroplasty: effects of epidural block on hip arthroplasty. *Journal of Clinical Anesthesia* 1997, **9**(3):200-3. *(Guideline Ref ID: DAUPHIN1997)*

125. Davies LM, Richardson GA, Cohen AT. Economic evaluation of enoxaparin as postdischarge prophylaxis for deep vein thrombosis (DVT) in elective hip surgery. *Value in Health* 2000, **3**(6):397-406. *(Guideline Ref ID: DAVIES2000)*

126. Davis FM, Laurenson VG. Spinal anaesthesia or general anaesthesia for emergency hip surgery in elderly patients. *Anaesthesia & Intensive Care* 1981, **9**(4):352-8. *(Guideline Ref ID: DAVIS1981)*

127. Davis FM, Laurenson VG, Gillespie WJ, Wells JE, Foate J, Newman E. Deep vein thrombosis after total hip replacement. A comparison between spinal and general anaesthesia. *Journal of Bone & Joint Surgery - British Volume* 1989, **71**(2):181-5. *(Guideline Ref ID: DAVIS1989)*

128. Dechavanne M, Saudin F, Viala JJ, Kher A, Bertrix L, de Mourgues G. (Prevention of venous thrombosis. Success of high doses of heparin during total hip replacement for osteoarthritis). *La Nouvelle presse médicale* 1974, **3**(20):1317-9. *(Guideline Ref ID: DECHAVANNE1974)*

129. Dechavanne M, Ville D, Berruyer M, Trepo F, Dalery F, Clermont N *et al*. Randomized trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. *Haemostasis* 1989, **19**(1):5-12. *(Guideline Ref ID: DECHAVANNE1989)*

130. Dechavanne M, Ville D, Viala JJ, Kher A, Faivre J, Pousset MB *et al*. Controlled trial of platelet anti-aggregating agents and subcutaneous heparin in prevention of postoperative deep vein thrombosis in high risk patients. *Haemostasis* 1975, **4**(2):94-100. *(Guideline Ref ID: DECHAVANNE1975)*

131. Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P *et al*. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. *New England Journal of Medicine* 1998, **338**(7):409-15. *(Guideline Ref ID: DECOUSUS1998)*

132. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Smith GD, Altman DG, eds. *Systematic reviews in health care: meta-analysis in context*, 15, 2001. pp 285-312. London: BMJ Publishing Group. *(Guideline Reference ID: Ref ID: DEEKS2001)*

133. Den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. *Journal of Thrombosis*

*and Haemostasis : JTH* 2005, **3**(2):292-9. *(Guideline Ref ID: DENHEIJER2005)*

134. Department of Health. (2005) NHS hospital episode statistics 2004-5. London: Department of Health. *(Guideline Ref ID: DH2005)*

135. Department of Health. (2006) NHS Reference Costs 2005. London: Department of Health. *(Guideline Ref ID: DH2006)*

136. Dickinson LD, Miller LD, Patel CP, Gupta SK. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. *Neurosurgery* 1998, **43**(5):1074-81. *(Guideline Ref ID: DICKINSON1998)*

137. DiSerio FJ, Sasahara AA. United States trial of dihydroergotamine and heparin prophylaxis of deep vein thrombosis. *American Journal of Surgery* 1985, **150**(4A):25-32. *(Guideline Ref ID: DISERIO1985A)*

138. Dranitsaris G, Kahn SR, Stumpo C, Paton TW, Martineau J, Smith R *et al*. Pharmacoeconomic analysis of fondaparinux versus enoxaparin for the prevention of thromboembolic events in orthopedic surgery patients. *American Journal of Cardiovascular Drugs* 2004, **4**(5):325-33. *(Guideline Ref ID: DRANITSARIS2004)*

139. Drummond M, Aristides M, Davies L, Forbes C. Economic evaluation of standard heparin and enoxaparin for prophylaxis against deep vein thrombosis in elective hip surgery. *British Journal of Surgery* 1994, **81**:1742-6. *(Guideline Ref ID: DRUMMOND1994)*

140. Ebaugh JL, Chiou AC, Morasch MD, Matsumura JS, Pearce WH. Bedside vena cava filter placement guided with intravascular ultrasound. *Journal of Vascular Surgery* 2001, **34**(1):21-6. *(Guideline Ref ID: EBAUGH2001)*

141. Eckman MH, Beshansky JR, Durand-Zaleski I, Levine HJ, Pauker SG. Anticoagulation for noncardiac procedures in patients with prosthetic heart valves. Does low risk mean high cost? *JAMA* 1990, **263**(11):1513-21. *(Guideline Ref ID: ECKMAN1990)*

142. Edmonds MJR, Crichton TJH, Runciman WB, Pradhan M. Evidence-based risk factors for postoperative deep vein thrombosis. *ANZ Journal of Surgery* 2004, **74**(12):1082-97. *(Guideline Ref ID: EDMONDS2004)*

143. Encke A, Breddin K. Comparison of a low molecular weight heparin and unfractionated heparin for the prevention of deep vein thrombosis in patients undergoing abdominal surgery. *British Journal of Surgery* 1988, **75**(11):1058-63. *(Guideline Ref ID: ENCKE1988)*

144. Encke A, Stock C, Dumke HO. Doppelblindstudie zur postoperativen thromboseprophylaxe mit dipyridamol/acetylsalicysaure. *Der Chirurg* 1976, **47**(12):670-3. *(Guideline Ref ID: ENCKE1976)*

145. Eriksson B, I, Kälebo P, Anthymyr BA, Wadenvik H, Tengborn L, Risberg B. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. Comparison of low-molecular-weight heparin and unfractionated heparin. *Journal of Bone and Joint Surgery* 1991, **73**(4):484-93. *(Guideline Ref ID: ERIKSSON1991A)*

146. Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *New England Journal of Medicine* 2001, **345**(18):1298-304. *(Guideline Ref ID: ERIKSSON2001)*

147. Eriksson BI, Lassen MR. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. *Archives of Internal Medicine* 2003, **163**(11):1337-42. *(Guideline Ref ID: ERIKSSON2003A)*

148. Eriksson BI, Zachrisson BE, Teger-Nilsson AC, Risberg B. Thrombosis prophylaxis with low molecular weight heparin in total hip replacement. *British Journal of Surgery* 1988, **75**(11):1053-7. *(Guideline Ref ID: ERIKSSON1988)*

149. Eskander MB, Limb D, Stone MH, Furlong AJ, Shardlow D, Stead D *et al*. Sequential mechanical and pharmacological thromboprophylaxis in the surgery of hip fractures. A pilot study. *International Orthopaedics* 1997, **21**(4):259-61. *(Guideline Ref ID: ESKANDER1997)*

150. Eskeland G, Solheim K, Skjorten F. Anticoagulant prophylaxis, thromboembolism and mortality in elderly patients with hip fractures. A controlled clinical trial. *Acta Chirurgica Scandinavica* 1966, **131**(1):16-29. *(Guideline Ref ID: ESKELAND1966)*

151. Etchells E, McLeod RS, Geerts W, Barton P, Detsky AS. Economic analysis of low-dose heparin vs the low-molecular weight heparin enoxaparin for prevention of venous thromboembolism after colorectal surgery. *Archives of Internal Medicine* 1999,

**159**(11):1221-8. *(Guideline Ref ID: ETCHELLS1999)*

152. Eurin B. (Efficacy and tolerance of Fraxiparine in the prevention of deep vein thrombosis in general surgery performed with medullar conduction anesthesia). *Annales françaises d'anesthèsie et de rèanimation* 1994, **13**(3):311-7. *(Guideline Ref ID: EURIN1994)*

153. Evarts CM, Feil EI, Alfidi RJ. Low molecular weight dextran to prevent venous thrombosis after elective surgery of the hip. A preliminary report. *Cleveland Clinic Quarterly* 1971, **38**(1):33-4. *(Guideline Ref ID: EVARTS1971)*

154. Faghri PD, Van Meerdervort HF, Glaser RM, Figoni SF. Electrical stimulation-induced contraction to reduce blood stasis during arthroplasty. *IEEE Trans Rehabil Eng* 1997, **5**(1):62-9. *(Guideline Ref ID: FAGHRI1997)*

155. Farkas JC, Chapuis C, Combe S, Silsiguen M, Marzelle J, Laurian C *et al.* A randomised controlled trial of a low-molecular-weight heparin (Enoxaparin) to prevent deep-vein thrombosis in patients undergoing vascular surgery. *European Journal of Vascular Surgery* 1993, **7**(5):554-60. *(Guideline Ref ID: FARKAS1993)*

156. Fasting H, Andersen K, Kraemmer-Nielsen H, Husted SE, Koopmann HD, Simonsen O *et al.* Prevention of postoperative deep venous thrombosis. Low-dose heparin versus graded pressure stockings. *Acta Chirurgica Scandinavica* 1985, **151**(3):245-8. *(Guideline Ref ID: FASTING1985)*

157. Faunø P, Suomalainen O, Rehnberg V, Hansen TB, Krøner K, Soimakallio S *et al.* Prophylaxis for the prevention of venous thromboembolism after total knee arthroplasty. A comparison between unfractionated and low-molecular-weight heparin. *Journal of Bone and Joint Surgery* 1994, **76**(12):1814-8. *(Guideline Ref ID: FAUNO1994)*

158. Feller JA, Parkin JD, Phillips GW, Hannon PJ, Hennessy O, Huggins RM. Prophylaxis against venous thrombosis after total hip arthroplasty. *Australian and New Zealand Journal of Surgery* 1992, **62**(8):606-10. *(Guideline Ref ID: FELLER1992)*

159. Fisher CG, Blachut PA, Salvian AJ, Meek RN, O'Brien PJ. Effectiveness of pneumatic leg compression devices for the prevention of thromboembolic disease in orthopaedic trauma patients: a prospective, randomized study of compression alone versus no prophylaxis. *Journal of Orthopaedic Trauma* 1995, **9**(1):1-7. *(Guideline Ref ID: FISHER1995)*

160. Fitzgerald RH, Jr., Spiro TE, Trowbridge AA, Gardiner GA, Jr., Whitsett TL, O'Connell MB *et al.* Prevention of venous thromboembolic disease following primary total knee arthroplasty. A randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. *Journal of Bone and Joint Surgery* 2001, **83-A**(6):900-6. *(Guideline Ref ID: FITZGERALD2001)*

161. Fletcher JP, Batiste P. Incidence of deep vein thrombosis following vascular surgery. *International Angiology* 1997, **16**(1):65-8. *(Guideline Ref ID: FLETCHER1997)*

162. Flicoteaux H, Kher A, Jean N, Blery M, Judet T, Honnart F *et al.* Comparision of low dose heparin and low dose heparin combined with aspirin in prevention of deep vein thrombosis after total hip replacement. *Pathologie Biologie* 1977, **25 Suppl**:55-8. *(Guideline Ref ID: FLICOTEAUX1977)*

163. Fordyce MJ, Baker AS, Staddon GE. Efficacy of fixed minidose warfarin prophylaxis in total hip replacement. *BMJ* 1991, **303**(6796):219-20. *(Guideline Ref ID: FORDYCE1991)*

164. Fordyce MJ, Ling RS. A venous foot pump reduces thrombosis after total hip replacement. *Journal of Bone and Joint Surgery British Volume* 1992, **74**(1):45-9. *(Guideline Ref ID: FORDYCE1992)*

165. Francis CW, Marder VJ, Evarts CM, Yaukoolbodi S. Two-step warfarin therapy. Prevention of postoperative venous thrombosis without excessive bleeding. *JAMA* 1983, **249**(3):374-8. *(Guideline Ref ID: FRANCIS1983)*

166. Francis CW, Pellegrini J, V, Marder VJ, Totterman S, Harris CM, Gabriel KR *et al.* Comparison of warfarin and external pneumatic compression in prevention of venous thrombosis after total hip replacement. *JAMA* 1992, **267**(21):2911-5. *(Guideline Ref ID: FRANCIS1992)*

167. Francis CW, Pellegrini VD, Leibert KM, Totterman S, Azodo MV, Harris CM *et al.* Comparison of two warfarin regimens in the prevention of venous thrombosis following total knee replacement. *Thrombosis and Haemostasis* 1996, **75**(5):706-11. *(Guideline Ref ID: FRANCIS1996)*

168. Francis CW, Pellegrini VD, Totterman S, Boyd AD, Marder VJ, Liebert KM *et al.* Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. *Journal of Bone and Joint Surgery*

*American Volume* 1997, **79**(9):1365-72. *(Guideline Ref ID: FRANCIS1997A)*

169. Francis CW, Pleil AM, Reinhart SP, Cohen B. A pharmacoeconomic evaluation of low-molecular-weight heparin in patients after total hip-replacement surgery. *P and T* 1999, **24**(3):136-45. *(Guideline Ref ID: FRANCIS1999)*

170. Fredin H, Bergqvist D, Cederholm C, Lindblad B, Nyman U. Thromboprophylaxis in hip arthroplasty. Dextran with graded compression or preoperative dextran compared in 150 patients. *Acta Orthopaedica Scandinavica* 1989, **60**(6):678-81. *(Guideline Ref ID: FREDIN1989)*

171. Fredin H, Nilsson B, Rosberg B, Tengborn L. Pre- and postoperative levels of antithrombin III with special reference to thromboembolism after total hip replacement. *Thrombosis and Haemostasis* 1983, **49**(3):158-61. *(Guideline Ref ID: FREDIN1983)*

172. Fredin H, Rosberg B. Anaesthetic techniques and thromboembolism in total hip arthroplasty. *European Journal of Anaesthesiology* 1986, **3**(4):273-81. *(Guideline Ref ID: FREDIN1986)*

173. Freick H, Haas S. Prevention of deep vein thrombosis by low-molecular-weight heparin and dihydroergotamine in patients undergoing total hip replacement. *Thrombosis Research* 1991, **63**(1):133-43. *(Guideline Ref ID: FREICK1991)*

174. Fricker JP, Vergnes Y, Schach R, Heitz A, Eber M, Grunebaum L *et al*. Low dose heparin versus low molecular weight heparin (Kabi 2165, Fragmin) in the prophylaxis of thromboembolic complications of abdominal oncological surgery. *European Journal of Clinical Investigation* 1988, **18**(6):561-7. *(Guideline Ref ID: FRICKER1988)*

175. Friedman RJ, Davidson BL, Heit J, Kessler C, Elliott CG. RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty. RD Heparin Arthroplasty Group. *Journal of Bone and Joint Surgery American Volume* 1994, **76**(8):1174-85. *(Guideline Ref ID: FRIEDMAN1994)*

176. Friedman RJ, Dunsworth GA. Cost analyses of extended prophylaxis with enoxaparin after hip arthroplasty. *Clinical Orthopaedics and Related Research* 2000, **370**:171-82. *(Guideline Ref ID: FRIEDMAN2000)*

177. Fuchs S, Heyse T, Rudofsky G, Gosheger G, Chylarecki C. Continuous passive motion in the prevention of deep-vein thrombosis: a randomised comparison in trauma patients. *Journal of Bone and Joint Surgery British Volume* 2005, **87**(8):1117-22. *(Guideline Ref ID: FUCHS2005A)*

178. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Archives of Internal Medicine* 1996, **156**(16):1829-36. *(Guideline Ref ID: GAGE1996)*

179. Galasko CS, Edwards DH, Fearn CB, Barber HM. The value of low dosage heparin for the prophylaxis of thromboembolism in patients with transcervical and intertrochanteric femoral fractures. *Acta Orthopaedica Scandinavica* 1976, **47**(3):276-82. *(Guideline Ref ID: GALASKO1976)*

180. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. *Blood* 2003, **101**(5):1827-32. *(Guideline Ref ID: GALLI2003)*

181. Gallus A, Cade J, Ockelford P, Hepburn S, Maas M, Magnani H *et al*. Orgaran (Org 10172) or heparin for preventing venous thrombosis after elective surgery for malignant disease? A double-blind, randomised, multicentre comparison. ANZ-Organon Investigators' Group. *Thrombosis and Haemostasis* 1993, **70**(4):562-7. *(Guideline Ref ID: GALLUS1993)*

182. Gallus A, Raman K, Darby T. Venous thrombosis after elective hip replacement--the influence of preventive intermittent calf compression and of surgical technique. *British Journal of Surgery* 1983, **70**(1):17-9. *(Guideline Ref ID: GALLUS1983)*

183. Gallus AS, Hirsh J, O'Brien SE, McBride JA, Tuttle RJ, Gent M. Prevention of venous thrombosis with small, subcutaneous doses of heparin. *JAMA* 1976, **235**(18):1980-2. *(Guideline Ref ID: GALLUS1976A)*

184. Gallus AS, Hirsh J, Tutle RJ, Trebilcock R, O'Brien SE, Carroll JJ *et al*. Small subcutaneous doses of heparin in prevention of venous thrombosis. *New England Journal of Medicine* 1973, **288**(11):545-51. *(Guideline Ref ID: GALLUS1973)*

185. Garcea D, Martuzzi F, Santelmo N, Savoia M, Casertano MG, Furno A *et al*. Post-surgical deep vein thrombosis prevention: evaluation of the risk/benefit ratio of fractionated and unfractionated heparin. *Current Medical*

*Research and Opinion* 1992, **12**(9):572-83. *(Guideline Ref ID: GARCEA1992)*

186. Garcia DA, Libby EN, Rich JS. Perioperative anticoagulation for patients with mechanical heart valves: A model comparing unfractionated and low-molecular-weight heparin. *Journal of Clinical Outcomes Management* 2005, **12**(1):25-31. *(Guideline Ref ID: GARCIA2005)*

187. Gardner AM, Fox RH. The venous pump of the human foot--preliminary report. *Bristol Med Chir J* 1983, **98**(367):109-12. *(Guideline Ref ID: GARDNER1983)*

188. Gazzaniga GM, Angelini G, Pastorino G, Santoro E, Lucchini M, Dal Pra ML. Enoxaparin in the prevention of deep venous thrombosis after major surgery: multicentric study. The Italian Study Group. *International Surgery* 1993, **78**(3):271-5. *(Guideline Ref ID: GAZZANIGA1993)*

189. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW *et al*. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004, **126**(3 Suppl):338S-400S. *(Guideline Ref ID: GEERTS2004)*

190. Gent M, Hirsh J, Ginsberg JS, Powers PJ, Levine MN, Geerts WH *et al*. Low-molecular-weight heparinoid orgaran is more effective than aspirin in the prevention of venous thromboembolism after surgery for hip fracture. *Circulation* 1996, **93**(1):80-4. *(Guideline Ref ID: GENT1996)*

191. Gerhart TN, Yett HS, Robertson LK, Lee MA, Smith M, Salzman EW. Low-molecular-weight heparinoid compared with warfarin for prophylaxis of deep-vein thrombosis in patients who are operated on for fracture of the hip. A prospective, randomized trial. *Journal of Bone and Joint Surgery American Volume* 1991, **73**(4):494-502. *(Guideline Ref ID: GERHART1991)*

192. Godwin JE, Comp P, Davidson B, Rossi M, Normiflo Cancer Clinical Trial Group. Comparison of the efficacy and safety of subcutaneous RD heparin vs subcutaneous unfractionated heparin for the prevention of deep-vein thrombosis in patients undergoing abdominal or pelvic surgery for cancer. *Thrombosis and Haemostasis* 1993, **69**(6):647. *(Guideline Ref ID: GODWIN1993)*

193. Goldhaber SZ, Dunn K, Gerhard-Herman M, Park JK, Black PM. Low rate of venous thromboembolism after craniotomy for brain tumor using multimodality prophylaxis. *Chest* 2002, **122**(6):1933-7. *(Guideline Ref ID: GOLDHABER2002)*

194. Goldhaber SZ, Hirsch DR, MacDougall RC, Polak JF, Creager MA, Cohn LH. Prevention of venous thrombosis after coronary artery bypass surgery (a randomized trial comparing two mechanical prophylaxis strategies). *American Journal of Cardiology* 1995, **76**(14):993-6. *(Guideline Ref ID: GOLDHABER1995)*

195. Gonzalez EM, Fontcuberta J, De l. Prophylaxis of thromboembolic disease with RO-11 (ROVI), during abdominal surgery. *Hepato Gastroenterology* 1996, **43**(9):744-7. *(Guideline Ref ID: GONZALEZ1996)*

196. Gordois A, Posnett J, Borris L, Bossuyt P, Jonsson B, Levy E *et al*. The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopedic surgery (Structured abstract). *Journal of Thrombosis and Haemostasis : JTH* 2003, **1**(10):2167-74. *(Guideline Ref ID: GORDOIS2003)*

197. Gordon-Smith IC, Hickman JA, el Masri SH. The effect of the fibrinolytic inhibitor epsilon-aminocaproic acid on the incidence of deep-vein thrombosis after prostatectomy. *British Journal of Surgery* 1972, **59**(7):522-4. *(Guideline Ref ID: GORDONSMITH1972A)*

198. Gordon-Smith IC, Le Quesne LP, Grundy DJ, Newcombe JF, Bramble FJ. Controlled trial of two regimens of subcutaneous heparin in prevention of postoperative deep-vein thrombosis. *The Lancet* 1972, **1**(7761):1133-5. *(Guideline Ref ID: GORDONSMITH1972)*

199. Goucke CR. Prophylaxis against venous thromboembolism. *Anaesth Intensive Care* 1989, **17**(4):458-65. *(Guideline Ref ID: GOUCKE1989)*

200. Government Actuary's Department. England and Wales interim life tables 2002-4 http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm *(Guideline Ref ID: GAD2005)*

201. Gozzard D, Hutchinson J, Lloyd A, Hutchings A. Economic evaluation of extended and conventional prophylaxis with enoxaparin against venous thromboembolism in patients undergoing surgery for abdominal cancer (Structured abstract). *Journal of Medical Economics* 2004, **7**:53-65. *(Guideline Ref ID: GOZZARD2004)*

202. Grieve R, Porsdal V, Hutton J, Wolfe C. A comparison of the cost-effectiveness of stroke care provided in London and Copenhagen.

*International Journal of Technology Assessment in Health Care* 2000, **16**(2):684-95. *(Guideline Ref ID: GRIEVE2000)*

203. Groote Schuur Hospital Thromboembolus Study Group. Failure of low-dose heparin to prevent significant thromboembolic complications in high-risk surgical patients: interim report of prospective trial. *British Medical Journal* 1979, **1**(6176):1447-50. *(Guideline Ref ID: ANON1979)*

204. Gruber UF, Duckert F, Fridrich R, Torhorst J, Rem J. Prevention of postoperative thromboembolism by dextran 40, low doses of heparin, or xantinol nicotinate. *The Lancet* 1977, **1**(8005):207-10. *(Guideline Ref ID: GRUBER1977A)*

205. Haas S, Stemberger A, Fritsche HM, Welzel D, Wolf H, Lechner F *et al*. Prophylaxis of deep vein thrombosis in high risk patients undergoing total hip replacement with low molecular weight heparin plus dihydroergotamine. *Arzneimittel-Forschung* 1987, **37**(7):839-43. *(Guideline Ref ID: HAAS1987)*

206. Haas S, Wolf H, Kakkar AK, Fareed J, Encke A. Prevention of fatal pulmonary embolism and mortality in surgical patients: a randomized double-blind comparison of LMWH with unfractionated heparin. *Thrombosis and Haemostasis* 2005, **94**(4):814-9. *(Guideline Ref ID: HAAS2005)*

207. Haas SB, Insall JN, Scuderi GR, Windsor RE, Ghelman B. Pneumatic sequential-compression boots compared with aspirin prophylaxis of deep-vein thrombosis after total knee arthroplasty. *Journal of Bone and Joint Surgery* 1990, **72**(1):27-31. *(Guideline Ref ID: HAAS1990)*

208. Haas SK, Wolf H, Encke A, Fareed J. Prevention of fatal postoperative pulmonary embolism by low molecular weight heparin. A double blind comparison of certoparin and unfractionated heparin. *Clinical and Applied Thrombosis/Hemostasis* 1999, **Suppl**:491. *(Guideline Ref ID: HAAS1999A)*

209. Haentjens P, De Groote K, Annemans L. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. A cost-utility analysis. *Archives of Orthopaedic and Trauma Surgery* 2004, **124**(8):507-17. *(Guideline Ref ID: HAENTJENS2004)*

210. Hamilton HW, Crawford JS, Gardiner JH, Wiley AM. Venous thrombosis in patients with fracture of the upper end of the femur. A phlebographic study of the effect of prophylactic anticoagulation. *Journal of Bone and Joint Surgery British Volume* 1970, **52**(2):268-89. *(Guideline Ref ID: HAMILTON1970)*

211. Hampson WG, Harris FC, Lucas HK, Roberts PH, McCall IW, Jackson PC *et al*. Failure of low-dose heparin to prevent deep-vein thrombosis after hip-replacement arthroplasty. *The Lancet* 1974, **2**(7884):795-7. *(Guideline Ref ID: HAMPSON1974A)*

212. Hamulyak K, Lensing AW, van der MJ, Smid WM, van Ooy A, Hoek JA. Subcutaneous low-molecular weight heparin or oral anticoagulants for the prevention of deep-vein thrombosis in elective hip and knee replacement? Fraxiparine Oral Anticoagulant Study Group. *Thrombosis and Haemostasis* 1995, **74**(6):1428-31. *(Guideline Ref ID: HAMULYAK1995)*

213. Hann CL, Streiff MB. The role of vena caval filters in the management of venous thromboembolism. *Blood Reviews* 2005, **19**(4):179-202. *(Guideline Ref ID: HANN2005)*

214. Hansberry KL, Thompson IM, Jr., Bauman J, Deppe S, Rodriguez FR. A prospective comparison of thromboembolic stockings, external sequential pneumatic compression stockings and heparin sodium /dihydroergotamine mesylate for the prevention of thromboembolic complications in urological surgery. *Journal of Urology* 1991, **145**(6):1205-8. *(Guideline Ref ID: HANSBERRY1991)*

215. Harris WH, Athanasoulis CA, Waltman AC, Salzman EW. Prophylaxis of deep-vein thrombosis after total hip replacement. Dextran and external pneumatic compression compared with 1.2 or 0.3 gram of aspirin daily. *Journal of Bone and Joint Surgery* 1985, **67**(1):57-62. *(Guideline Ref ID: HARRIS1985)*

216. Harris WH, Salzman EW, Athanasoulis C, Waltman AC, Baum S, DeSanctis RW. Comparison of warfarin, low-molecular-weight dextran, aspirin, and subcutaneous heparin in prevention of venous thromboembolism following total hip replacement. *Journal of Bone and Joint Surgery* 1974, **56**(8):1552-62. *(Guideline Ref ID: HARRIS1974)*

217. Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, DeSanctis RW. Aspirin prophylaxis of venous thromboembolism after total hip replacement. *New England Journal of Medicine* 1977, **297**(23):1246-9. *(Guideline Ref ID: HARRIS1977)*

218. Harris WH, Salzman EW, DeSanctis RW, Coutts RD. Prevention of venous thromboembolism following total hip replacement. Warfarin vs dextran 40. *JAMA* 1972, **220**(10):1319-22. *(Guideline Ref ID: HARRIS1972)*

219. Hartl P, Brucke P, Dienstl E, Vinazzer H. Prophylaxis of thromboembolism in general surgery: comparison between standard heparin and Fragmin. *Thrombosis Research* 1990, **57**(4):577-84. *(Guideline Ref ID: HARTL1990)*

220. Hauch O, Jorgensen LN, Kolle TR, Nerstrom H, Schebye O, Wille-Jorgensen P *et al*. Low molecular weight heparin (Logiparin(TM)) as thromboprophylaxis in elective abdominal surgery. A dose finding study. *Acta Chirurgica Scandinavica* 1988, **154**(Suppl 543):90-5. *(Guideline Ref ID: HAUCH1988)*

221. Hawkins D. Pharmacoeconomics of thrombosis management. *Pharmacotherapy* 2004, **24**(7 Pt 2):95S-9S. *(Guideline Ref ID: HAWKINS2004)*

222. Hawkins DW, Langley PC, Kruegar KP. Pharmacoeconomic model of enoxaparin versus heparin for prevention of deep vein thrombosis after total hip replacement. *American Journal of Health-System Pharmacy* 1997, **54**(10):1185-90. *(Guideline Ref ID: HAWKINS1997)*

223. Hawkins DW, Langley PC, Krueger KP. A pharmacoeconomic assessment of enoxaparin and warfarin as prophylaxis for deep vein thrombosis in patients undergoing knee replacement surgery. *Clinical Therapeutics* 1998, **20**(1):182-95. *(Guideline Ref ID: HAWKINS1998)*

224. Heaton D, Pearce M. Low molecular weight versus unfractioned herapin: a clinical and economic appraisal. *Pharmacoeconomics* 1995, **8**(2):91-9. *(Guideline Ref ID: HEATON1995)*

225. Hedlund PO, Blombäck M. The effect of prophylaxis with low dose heparin on blood coagulation parameters. A double blind study in connection with transvesical prostatectomy. *Thrombosis and Haemostasis* 1979, **41**(2):337-45. *(Guideline Ref ID: HEDLUND1979)*

226. Hedlund PO, Blombäck M. The effects of low-dose heparin treatment on patients undergoing transvesical prostatectomy. *Urological Research* 1981, **9**(3):147-52. *(Guideline Ref ID: HEDLUND1981)*

227. Heerey A, Suri S. Cost effectiveness of dalteparin for preventing venous thromboembolism in abdominal surgery. *Pharmacoeconomics* 2005, **23**(9):927-44. *(Guideline Ref ID: HEEREY2005)*

228. Hefley WF, Nelson CL, Puskarich CL. Thromboembolic disease in patients with fractures of the hip: preoperative prevalence and effect of dextran prophylaxis. *Southern Medical Journal* 1990, **83**:S49-S50. *(Guideline Ref ID: HEFLEY1990)*

229. Heilmann L, Kruck M, Schindler AE. (Prevention of thrombosis in gynecology: double-blind comparison of low molecular weight heparin and unfractionated heparin). *Geburtshilfe und Frauenheilkunde* 1989, **49**(9):803-7. *(Guideline Ref ID: HEILMANN1989)*

230. Heilmann L, von Tempelhoff GF, Kirkpatrick C, Schneider DM, Hommel G, Pollow K. Comparison of unfractionated versus low molecular weight heparin for deep vein thrombosis prophylaxis during breast cancer surgery: efficacy, safety, and follow-up. *Clinical and Applied Thrombosis/Hemostasis* 1998, **4**(4):268-73. *(Guideline Ref ID: HEILMANN1998)*

231. Heilmann L, von Tempelhoff G-F, Herrle B, Hojnacki B, Schneider D, Michaelis HC *et al*. (Prevention of postoperative venous thrombosis. A randomized trial comparing low-dose heparin and low molecular weight heparin in gynaecological oncology). *Geburtshilfe und Frauenheilkunde* 1997, **57**(1):1-6. *(Guideline Ref ID: HEILMANN1997)*

232. Heit JA, Elliott CG, Trowbridge AA, Morrey BF, Gent M, Hirsh J. Ardeparin sodium for extended out-of-hospital prophylaxis against venous thromboembolism after total hip or knee replacement. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 2000, **132**(11):853-61. *(Guideline Ref ID: HEIT2000A)*

233. Heit JA, Scott D, Berkowitz SD, Bona R, Cabanas V, Corson JD *et al*. Efficacy and safety of low molecular weight heparin (ardeparin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: A double- blind dose-ranging study. *Thrombosis and Haemostasis* 1997, **77**(1):32-8. *(Guideline Ref ID: HEIT1997)*

234. Hendolin H, Mattila MA, Poikolainen E. The effect of lumbar epidural analgesia on the development of deep vein thrombosis of the legs after open prostatectomy. *Acta Chirurgica Scandinavica* 1981, **147**(6):425-9. *(Guideline Ref ID: HENDOLIN1981)*

235. Hendolin H, Tuppurainen T, Lahtinen J. Thoracic epidural analgesia and deep vein thrombosis in cholecystectomized patients. *Acta Chirurgica*

*Scandinavica* 1982, **148**(5):405-9. *(Guideline Ref ID: HENDOLIN1982)*

236. Hills NH, Pflug JJ, Jeyasingh K, Boardman L, Calnan JS. Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. *BMJ* 1972, **1**(793):131-5. *(Guideline Ref ID: HILLS1972)*

237. Ho YK, Seow-Choen F, Leong A, Eu KW, Nyam D, Teoh MK. Randomized, controlled trial of low molecular weight heparin vs. no deep vein thrombosis prophylaxis for major colon and rectal surgery in Asian patients. *Diseases of the Colon and Rectum* 1999, **42**(2):196-203. *(Guideline Ref ID: HO1999)*

238. Hodge WA. Prevention of deep vein thrombosis after total knee arthroplasty. Coumadin versus pneumatic calf compression. *Clinical Orthopaedics and Related Research* 1991,(271):101-5. *(Guideline Ref ID: HODGE1991)*

239. Hoek JA, Nurmohamed MT, Hamelynck KJ, Marti RK, Knipscheer HC, ten Cate H *et al*. Prevention of deep vein thrombosis following total hip replacement by low molecular weight heparinoid. *Thrombosis and Haemostasis* 1992, **67**(1):28-32. *(Guideline Ref ID: HOEK1992)*

240. Hoffman R, Largiadèr F, Brütsch HP. (Perioperative thromboembolic prophylaxis with low molecular weight heparin and postoperative bleeding complications). *Langenbecks Archiv fur Chirurgie* 1990, **Suppl II**:1179-84. *(Guideline Ref ID: HOFFMANN1990)*

241. Hoffmann R. The thrombo-embolic risk in surgery. *Hepato-Gastroenterology* 1991, **38**(4):272-8. *(Guideline Ref ID: HOFFMANN1991)*

242. Hoffmann R, Largiader F. (Perioperative prevention of thromboembolism with standard heparin and low molecular weight heparin, evaluation of postoperative hemorrhage. A double-blind, prospective, randomized and mono-center study). *Langenbecks Archiv fur Chirurgie* 1992, **377**(5):258-61. *(Guideline Ref ID: HOFFMANN1992)*

243. Hohl MK, Luscher KP, Tichy J, Stiner M, Fridrich R, Gruber UF *et al*. Prevention of postoperative thromboembolism by dextran 70 or low-dose heparin. *Obstetrics and Gynecology* 1980, **55**(4):497-500. *(Guideline Ref ID: HOHL1980)*

244. Holford CP. Graded compression for preventing deep venous thrombosis. *BMJ* 1976, **2**(6042):969-70. *(Guideline Ref ID: HOLFORD1976)*

245. Horbach T, Wolf H, Michaelis HC, Wagner W, Hoffmann A, Schmidt A *et al*. A fixed-dose combination of low molecular weight heparin with dihydroergotamine versus adjusted-dose unfractionated heparin in the prevention of deep-vein thrombosis after total hip replacement. *Thrombosis and Haemostasis* 1996, **75**(2):246-50. *(Guideline Ref ID: HORBACH1996)*

246. House of Commons Health Committee. (2005) The prevention of venous thromboembolism in hospitalised patients. London: The Stationery Office Limited. *(Guideline Ref ID: HOUSEOFCOMMONS2005)*

247. Howard A, Zaccagnini D, Ellis M, Williams A, Davies AH, Greenhalgh RM. Randomized clinical trial of low molecular weight heparin with thigh-length or knee-length antiembolism stockings for patients undergoing surgery. *British Journal of Surgery* 2004, **91**(7):842-7. *(Guideline Ref ID: HOWARD2004)*

248. Howie C, Hughes H, Watts AC. Venous thromboembolism associated with hip and knee replacement over a ten-year period: a population-based study. *Journal of Bone and Joint Surgery British Volume* 2005, **87**(12):1675-80. *(Guideline Ref ID: HOWIE2005)*

249. Hubens A, Peeters R. (The case for more active prevention of deep-vein thrombosis after major surgery). *Acta Chirurgica Belgica* 1976, **75**(4):402-15. *(Guideline Ref ID: HUBENS1976)*

250. Hui AC, Heras-Palou C, Dunn I, Triffitt PD, Crozier A, Imeson J *et al*. Graded compression stockings for prevention of deep-vein thrombosis after hip and knee replacement. *Journal of Bone and Joint Surgery British Volume* 1996, **78**(4):550-4. *(Guideline Ref ID: HUI1996)*

251. Hull R, Delmore TJ, Hirsch J, Gent M, Armstrong P, Lofthouse R *et al*. Effectiveness of intermittent pulsative elastic stockings for the prevention of calf and thigh vein thrombosis in patients undergoing elective knee surgery. *Thrombosis Research* 1979, **16**(1-2):37-45. *(Guideline Ref ID: HULL1979)*

252. Hull R, Raskob G, Pineo G, Rosenbloom D, Evans W, Mallory T *et al*. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *New England Journal of Medicine* 1993, **329**(19):1370-6. *(Guideline Ref ID: HULL1993)*

253. Hull RD, Hirsh J, Sackett DL, Stoddart GL. Cost-effectiveness of primary and secondary prevention of fatal pulmonary embolism in high-risk surgical patients. *Canadian Medical Association Journal* 1982, **127**(10):990-5. *(Guideline Ref ID: HULL1982)*

254. Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K *et al*. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. North American Fragmin Trial Investigators. *Archives of Internal Medicine* 2000, **160**(14):2208-15. *(Guideline Ref ID: HULL2000A)*

255. Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K *et al*. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. The North American Fragmin Trial Investigators. *Archives of Internal Medicine* 2000, **160**(14):2199-207. *(Guideline Ref ID: HULL2000)*

256. Hull RD, Pineo GF, Stein PD, Mah AF, MacIsaac SM, Dahl OE *et al*. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Annals of Internal Medicine* 2001, **135**(10):858-69. *(Guideline Ref ID: HULL2001)*

257. Hull RD, Pineo GF, Stein PD, Mah AF, MacIsaac SM, Dahl OE *et al*. Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: a systematic review. *Archives of Internal Medicine* 2001, **161**(16). *(Guideline Ref ID: HULL2001A)*

258. Hull RD, Raskob GE, Gent M, McLoughlin D, Julian D, Smith FC *et al*. Effectiveness of intermittent pneumatic leg compression for preventing deep vein thrombosis after total hip replacement. *JAMA* 1990, **263**(17):2313-7. *(Guideline Ref ID: HULL1990)*

259. Hull RD, Raskob GE, Pineo GF, Feldstein W, Rosenbloom D, Gafni A *et al*. Subcutaneous low-molecular-weight heparin vs warfarin for prophylaxis of deep vein thrombosis after hip or knee implantation: an economic perspective. *Archives of Internal Medicine* 1997, **157**(3):298-303. *(Guideline Ref ID: HULL1997)*

260. Hume M, Kuriakose TX, Zuch L, Turner RH. 125I fibrinogen and the prevention of venous thrombosis. *Archives of Surgery* 1973, **107**(5):803-6. *(Guideline Ref ID: HUME1973)*

261. Hurson B, Ennis JT, Corrigan TP, MacAuley P. Dextran prophylaxis in total hip replacement: a scintigraphic evaluation of the incidence of deep vein thrombosis and pulmonary embolus. *Irish Journal of Medical Science* 1979, **148**(4):140-4. *(Guideline Ref ID: HURSON1979)*

262. Huttunen H, Mattila MA, Alhava EM, Kettunen K, Karjalainen P, Poikolainen P *et al*. Peroperative infusion of dextran 70 and dextran 40 in the prevention of postoperative deep venous thrombosis as confirmed by the I-125-labelled fibrinogen uptake method. *Annales Chirurgiae et Gynaecologiae* 1977, **66**(2):79-81. *(Guideline Ref ID: HUTTUNEN1977)*

263. Hye RJ, Mitchell AT, Dory CE, Freischlag JA, Roberts AC. Analysis of the transition to percutaneous placement of Greenfield filters. *Archives of Surgery* 1990, **125**(12):1550-3. *(Guideline Ref ID: HYE1990)*

264. Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: a meta-analysis. *Archives of Internal Medicine* 2000, **160**(15):2327-32. *(Guideline Ref ID: IORIO2000)*

265. Janvrin SB, Davies G, Greenhalgh RM. Postoperative deep vein thrombosis caused by intravenous fluids during surgery. *British Journal of Surgery* 1980, **67**(10):690-3. *(Guideline Ref ID: JANVRIN1980)*

266. Joffe SN. Incidence of postoperative deep vein thrombosis in neurosurgical patients. *Journal of Neurosurgery* 1975, **42**(2):201-3. *(Guideline Ref ID: JOFFE1975A)*

267. Johnsson SR, Bygdeman S, Eliasson R. Effect of dextran on postoperative thrombosis. *Acta Chirurgica Scandinavica Supplementum* 1968, **387**:80-2. *(Guideline Ref ID: JOHNSSON1968)*

268. Joint Formulary Committee. (2006) British National Formulary. London: British Medical Association and Royal Pharmaceutical Society of Great Britain. *(Guideline Ref ID: BNF2006)*

269. Jorgensen JO, Lalak NJ, North L, Hanel K, Hunt DR, Morris DL. Venous stasis during laparoscopic cholecystectomy. *Surg Laparosc Endosc* 1994, **4**(2):128-33. *(Guideline Ref ID: JORGENSEN1994)*

270. Jorgensen LN, Rasmussen LS, Nielsen PT, Leffers A, Albrecht-Beste E. Antithrombotic efficacy of continuous extradural analgesia after knee replacement. *British Journal of Anaesthesia*

1991, **66**(1):8-12. *(Guideline Ref ID: JORGENSEN1991)*

271. Jørgensen PS, Knudsen JB, Broeng L, Josephsen L, Bjerregaard P, Hagen K *et al*. The thromboprophylactic effect of a low-molecular-weight heparin (Fragmin) in hip fracture surgery. A placebo-controlled study. *Clinical Orthopaedics and Related Research* 1992,(278):95-100. *(Guideline Ref ID: JØRGENSEN1992)*

272. Josefsson G, Dahlqvist A, Bodfors B. Prevention of thromboembolism in total hip replacement. Aspirin versus dihydroergotamine-heparin. *Acta Orthopaedica Scandinavica* 1987, **58**(6):626-9. *(Guideline Ref ID: JOSEFSSON1987)*

273. Jourdan M, McColl I. The use of prophylactic subcutaneous heparin in patients undergoing hernia repairs. *British Journal of Clinical Practice* 1984, **38**(9):298-300. *(Guideline Ref ID: JOURDAN1984)*

274. Kaaja R, Lehtovirta P, Venesmaa P, Kajanoja P, Halonen P, Gummerus M *et al*. Comparison of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin, with or without dihydroergotamine, in abdominal hysterectomy. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 1992, **47**(2):141-5. *(Guideline Ref ID: KAAJA1992)*

275. Kaempffe FA, Lifeso RM, Meinking C. Intermittent pneumatic compression versus coumadin. Prevention of deep vein thrombosis in lower-extremity total joint arthroplasty. *Clinical Orthopaedics and Related Research* 1991,(269):89-97. *(Guideline Ref ID: KAEMPFFE1991)*

276. Kakkar AK, Davidson BL, Haas SK, The Investigators Against Thromboembolism (INATE) Core Group. Compliance with recommended prophylaxis for venous thromboembolism: improving the use and rate of uptake of clinical practice guidelines. *Journal of Thrombosis and Haemostasis : JTH* 2004, **2**(2):221-7. *(Guideline Ref ID: KAKKAR2004)*

277. Kakkar VV, Boeckl O, Boneu B, Bordenave L, Brehm OA, Brucke P *et al*. Efficacy and safety of a low-molecular-weight heparin and standard unfractionated heparin for prophylaxis of postoperative venous thromboembolism: European multicenter trial. *World Journal of Surgery* 1997, **21**(1):2-8. *(Guideline Ref ID: KAKKAR1997)*

278. Kakkar VV, Cohen AT, Edmonson RA, Phillips MJ, Cooper DJ, Das SK *et al*. Low molecular weight versus standard herapin for prevention of venous thromboembolism after major abdominal surgery. *The Lancet* 1993, **341**(8840):259-65. *(Guideline Ref ID: KAKKAR1993)*

279. Kakkar VV, Cohen AT, Mohamed MS. Patients at risk of venous thromboembolism -- clinical results with reviparin. *Thrombosis Research* 1996, **81**(2 Suppl):S39-S45. *(Guideline Ref ID: KAKKAR1996A)*

280. Kakkar VV, Corrigan T, Spindler J, Fossard DP, Flute PT, Crellin RQ *et al*. Efficacy of low doses of heparin in prevention of deep-vein thrombosis after major surgery. A double-blind, randomised trial. *The Lancet* 1972, **2**(7768):101-6. *(Guideline Ref ID: KAKKAR1972)*

281. Kakkar VV, Howes J, Sharma V, Kadziola Z. A comparative double-blind, randomised trial of a new second generation LMWH (bemiparin) and UFH in the prevention of post-operative venous thromboembolism. The Bemiparin Assessment group. *Thrombosis and Haemostasis* 2000, **83**(4):523-9. *(Guideline Ref ID: KAKKAR2000)*

282. Kakkar VV, Murray WJ. Efficacy and safety of low-molecular-weight heparin (CY216) in preventing postoperative venous thrombo-embolism: a co-operative study. *British Journal of Surgery* 1985, **72**(10):786-91. *(Guideline Ref ID: KAKKAR1985)*

283. Kakkar VV, Stringer MD, Hedges AR, Parker CJ, Welzel D, Ward VP *et al*. Fixed combinations of low-molecular weight or unfractionated heparin plus dihydroergotamine in the prevention of postoperative deep vein thrombosis. *American Journal of Surgery* 1989, **157**(4):413-8. *(Guideline Ref ID: KAKKAR1989)*

284. Kalodiki EP, Hoppensteadt DA, Nicolaides AN, Fareed J, Gill K, Regan F *et al*. Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. A randomised controlled trial. *International Angiology* 1996, **15**(2):162-8. *(Guideline Ref ID: KALODIKI1996)*

285. Keeling D, Davidson S, Watson H. The management of heparin-induced thrombocytopenia. *British Journal of Haematology* 2006, **133**(3):259-69. *(Guideline Ref ID: KEELING2006)*

286. Keeling DM, Mackie IJ, Moody A, Watson HG, The Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The diagnosis of deep vein thrombosis in symptomatic outpatients and the

potential for clinical assessment and D-dimer assays to reduce the need for diagnostic imaging. *British Journal of Haematology* 2004, **124**(1):15-25. *(Guideline Ref ID: KEELING2004)*

287. Keeney JA, Clohisy JC, Curry MC, Maloney WJ. Efficacy of Combined Modality Prophylaxis Including Short-Duration Warfarin to Prevent Venous Thromboembolism After Total Hip Arthroplasty. *Journal of Arthroplasty* 2006, **21**(4):469-75. *(Guideline Ref ID: KEENEY2006)*

288. Kelly J, Hunt BJ, Lewis RR, Swaminathan R, Moody A, Seed PT *et al*. Dehydration and venous thromboembolism after acute stroke. *QJM* 2004, **97**(5):293-6. *(Guideline Ref ID: KELLY2004)*

289. Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. *BMJ* 2001, **323**(7305):131-4. *(Guideline Ref ID: KEMMEREN2001)*

290. Kettunen K, Poikolainen E, Karjalainen P, Oksala I, Alhava E, Rehnberg V *et al*. (Prevention of postoperative deep vein thrombosis with small doses of heparin). *Duodecim* 1974, **90**(11):834-8. *(Guideline Ref ID: KETTUNEN1974)*

291. Kierkegaard A, Norgren L, Olsson CG, Castenfors J, Persson G, Persson S. Incidence of deep vein thrombosis in bedridden non-surgical patients. *Acta Med Scand* 1987, **222**(5):409-14. *(Guideline Ref ID: KIERKEGAARD1987)*

292. Kiil J, Jensen FT. (The incidence of postoperative pulmonary embolism and the influence of heparin in low dosages on this as assessed by ventilation-perfusion scintigraphy). *Ugeskrift for Laeger* 1978, **140**(21):1215-7. *(Guideline Ref ID: KIIL1978B)*

293. Kiil J, Kiil J, Axelsen F. (Heparin in low dosage as prophylaxis of postoperative pulmonary embolism and deep venous thrombosis). *Ugeskrift for Laeger* 1978, **140**(21):1224-30. *(Guideline Ref ID: KIIL1978)*

294. Kiil J, Kiil J, Axelsen F, Andersen D. Prophylaxis against postoperative pulmonary embolism and deep-vein thrombosis by low-dose heparin. *The Lancet* 1978, **1**(8074):1115-6. *(Guideline Ref ID: KIIL1978G)*

295. Kiil J, Moller JC. (Postoperative deep thrombosis in the lower limbs and the prophylactic value of heparin in low dosage as assessed by phlebography). *Ugeskrift for Laeger* 1978, **140**(21):1221-4. *(Guideline Ref ID: KIIL1978A)*

296. Kiil J, Møoller JC. Postoperative deep vein thrombosis of the lower limb and prophylactic value of heparin evaluated by phlebography. *Acta Radiologica: Diagnosis* 1979, **20**(3):507-12. *(Guideline Ref ID: KIIL1979)*

297. Killewich LA, Aswad MA, Sandager GP, Lilly MP, Flinn WR. A randomized, prospective trial of deep venous thrombosis prophylaxis in aortic surgery. *Archives of Surgery* 1997, **132**(5):499-504. *(Guideline Ref ID: KILLEWICH1997)*

298. Killewich LA, Cahan MA, Hanna DJ, Murakami M, Uchida T, Wiley LA *et al*. The effect of external pneumatic compression on regional fibrinolysis in a prospective randomized trial. *Journal of Vascular Surgery* 2002, **36**(5):953-8. *(Guideline Ref ID: KILLEWICH2002)*

299. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998, **316**(7133):736-41. *(Guideline Ref ID: KIND1998)*

300. Koch A, Bouges S, Ziegler S, Dinkel H, Daures JP, Victor N. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. *British Journal of Surgery* 1997, **84**(6):750-9. *(Guideline Ref ID: KOCH1997)*

301. Kolb G, Bodamer I, Galster H, Seidlmayer C, Grambach K, Koudela K *et al*. Reduction of venous thromboembolism following prolonged prophylaxis with the low molecular weight heparin Certoparin after endoprothetic joint replacement or osteosynthesis of the lower limb in elderly patients. *Thrombosis and Haemostasis* 2003, **90**(6):1100-5. *(Guideline Ref ID: KOLB2003)*

302. Koller M, Schoch U, Buchmann P, Largiadèr F, Von Felten A, Frick PG. Low molecular weight heparin (KABI 2165) as thromboprophylaxis in elective visceral surgery. A randomized, double-blind study versus unfractionated heparin. *Thrombosis and Haemostasis* 1986, **56**(3):243-6. *(Guideline Ref ID: KOLLER1986)*

303. Koppenhagen K, Adolf J, Matthes M, Troster E, Roder JD, Hass S *et al*. Low molecular weight heparin and prevention of postoperative thrombosis in abdominal surgery. *Thrombosis and Haemostasis* 1992, **67**(6):627-30. *(Guideline Ref ID: KOPPENHAGEN1992)*

304. Koppenhagen K, Matthes M. (Heparin-dihydergot or heparin alone in thrombosis prophylaxis?). *Medizinische Welt* 1982, **33**(6):216-23. *(Guideline Ref ID: KOPPENHAGEN1982)*

305. Koppenhagen K, Matthes M, Haering R, Troester E, Wolf H, Welzel D. (Prophylaxis of thromboembolism in elective abdominal surgery: comparison of efficiacy and safety of low molecular weight heparin and unfractionated heparin). *Munchener Medizinische Wochenschrift* 1990, **132**(43):677-80. *(Guideline Ref ID: KOPPENHAGEN1990)*

306. Korvald E, Storen EJ, Ongre A. Simultaneous use of warfarin-sodium and dextran 70 to prevent post-operative venous thrombosis in patients with hip fractures. A controlled trial. *Journal of the Oslo City Hospitals* 1973, **23**(2):25-34. *(Guideline Ref ID: KORVALD1973)*

307. Kosir MA, Schmittinger L, Barno WL, Duddella P, Pone M, Perales A *et al*. Prospective double-arm study of fibrinolysis in surgical patients. *Journal of Surgical Research* 1998, **74**(1):96-101. *(Guideline Ref ID: KOSIR1998)*

308. Kraytman M, Kutnowski M, Ansay J. (Prevention of postoperative venous thrombosis with low dose subcutaneous heparin therapy). *Acta Clinica Belgica* 1977, **32**(6):422-7. *(Guideline Ref ID: KRAYTMAN1977)*

309. Kraytman M, Kutnowski M, Ansay J, Fastrez R. (Prophylaxis of postoperative deep vein thromboses by means of weak doses of subcutaneous heparin). *Acta Chirurgica Belgica* 1976, **75**(5):519-29. *(Guideline Ref ID: KRAYTMAN1976)*

310. Kruse-Blinkenberg HO, Gormsen J. The influence of low dose heparin in elective surgery on blood coagulation, fibrinolysis, platelet function, antithrombin III and antiplasmin. *Acta Chirurgica Scandinavica* 1980, **146**(6):375-82. *(Guideline Ref ID: KRUSEBLINKENBER1980)*

311. Kutnowski M, Vandendris M, Steinberger R, Kraytman M. Prevention of postoperative deep-vein thrombosis by low-dose heparin in urological surgery. A double-blind, randomised study. *Urological Research* 1977, **5**(3):123-5. *(Guideline Ref ID: KUTNOWSKI1977)*

312. Lahnborg G. Effect of low-dose heparin and dihydroergotamine on frequency of postoperative deep-vein thrombosis in patients undergoing post-traumatic hip surgery. *Acta Chirurgica Scandinavica* 1980, **146**(5):319-22. *(Guideline Ref ID: LAHNBORG1980)*

313. Lahnborg G, Bergström K. Clinical and haemostatic parameters related to thromboembolism and low-dose heparin prophylaxis in major surgery. *Acta Chirurgica Scandinavica* 1975, **141**(7):590-5. *(Guideline Ref ID: LAHNBORG1975)*

314. Lahnborg G, Bergstrom K, Friman L, Lagergren H. Effect of low dose heparin on incidence of postoperative pulmonary embolism detected by photoscanning. *The Lancet* 1974, **1**(7853):329-31. *(Guideline Ref ID: LAHNBORG1974)*

315. Lahnborg G, Lagergren H, Hedenstierna G. Effect of low-dose heparin prophylaxis on arterial oxygen tension after high laparotomy. *The Lancet* 1976, **1**(7950):54-6. *(Guideline Ref ID: LAHNBORG1976)*

316. Lambie JM, Barber DC, Dhall DP, Matheson NA. Dextran 70 in prophylaxis of postoperative venous thrombosis. A controlled trial. *BMJ* 1970, **2**(702):144-5. *(Guideline Ref ID: LAMBIE1970)*

317. Lassen MR, Bauer KA, Eriksson BI, Turpie AGG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *The Lancet* 2002, **359**(9319):1715-20. *(Guideline Ref ID: LASSEN2002)*

318. Lassen MR, Borris LC, Anderson BS, Jensen HP, Skejø Bro HP, Andersen G *et al*. Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty--the Danish Prolonged Prophylaxis (DaPP) Study. *Thrombosis Research* 1998, **89**(6):281-7. *(Guideline Ref ID: LASSEN1998)*

319. Lassen MR, Borris LC, Christiansen HM, Boll KL, Eiskjaer SP, Nielsen BW *et al*. Prevention of thromboembolism in 190 hip arthroplasties. Comparison of LMW heparin and placebo. *Acta Orthopaedica Scandinavica* 1991, **62**(1):33-8. *(Guideline Ref ID: LASSEN1991)*

320. Lassen MR, Borris LC, Christiansen HM, Møller LF, Knudsen VE, Boris P *et al*. Heparin/dihydroergotamine for venous thrombosis prophylaxis: comparison of low-dose heparin and low molecular weight heparin in hip surgery. *British Journal of Surgery* 1988, **75**(7):686-9. *(Guideline Ref ID: LASSEN1988)*

321. Lassen MR, Borris LC, Christiansen HM, Møller LF, Knudsen VE, Boris P *et al*. Prevention of thromboembolism in hip-fracture patients. Comparison of low-dose heparin and low-molecular-weight heparin combined with dihydroergotamine. *Archives of Orthopaedic and Trauma Surgery* 1989, **108**(1):10-3. *(Guideline Ref ID: LASSEN1989)*

322. Lastória S, Rollo HA, Yoshida WB, Giannini M, Moura R, Maffei F-HA. Prophylaxis of deep-vein thrombosis after lower extremity amputation. Comparison of low molecular weight heparin with unfractionated heparin. *Acta Cirurgica Brasileira* 2006, **21**(3):184-6. *(Guideline Ref ID: LASTORIA2006)*

323. Lausen I, Jensen R, Jorgensen LN, Rasmussen MS, Lyng KM, Andersen M *et al*. Incidence and prevention of deep venous thrombosis occurring late after general surgery: randomised controlled study of prolonged thromboprophylaxis. *European Journal of Surgery* 1998, **164**(9):657-63. *(Guideline Ref ID: LAUSEN1998A)*

324. Lawrence JC, Xabregas A, Gray L, Ham JM. Seasonal variation in the incidence of deep vein thrombosis. *British Journal of Surgery* 1977, **64**(11):777-80. *(Guideline Ref ID: LAWRENCE1977)*

325. Le Gagneux F, Steg A, Le Guillou M. Subcutaneous enoxaparine (Lovenox) versus placebo for preventing deep vein thrombosis (DVT) after transurethral prostatectomy (TUP). *Thrombosis and Haemostasis* 1987, **58**:116. *(Guideline Ref ID: LEGAGNEUX1987)*

326. Leclerc JR, Geerts WH, Desjardins L, Jobin F, Laroche F, Delorme F *et al*. Prevention of deep vein thrombosis after major knee surgery -- a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. *Thrombosis and Haemostasis* 1992, **67**(4):417-23. *(Guideline Ref ID: LECLERC1992)*

327. Leclerc JR, Geerts WH, Desjardins L, Laflamme GH, L'Espérance B, Demers C *et al*. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. *Annals of Internal Medicine* 1996, **124**(7):619-26. *(Guideline Ref ID: LECLERC1996)*

328. Legnani C, Maccaferri M, Palareti G, Ludovici S, Guazzaloca G, Marabini A *et al*. Perioperative prophylaxis with a low molecular weight heparin reduces late PAI-1 levels after gynaecological surgery. *Fibrinolysis* 1990, **4**(4):241-5. *(Guideline Ref ID: LEGNANI1990)*

329. Leizorovicz A, Picolet H, Peyrieux JC, Boissel JP. Prevention of perioperative deep vein thrombosis in general surgery: a multicentre double blind study comparing two doses of Logiparin and standard heparin. H.B.P.M. Research Group. *British Journal of Surgery* 1991, **78**(4):412-6. *(Guideline Ref ID: LEIZOROVICZ1991)*

330. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. *Journal of the American Medical Informatics Association* 1997, **4**(1):49-56. *(Guideline Ref ID: LENERT1997)*

331. Levine MN, Gent M, Hirsh J, Weitz J, Turpie AG, Powers P *et al*. Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism. A randomized trial in patients undergoing knee surgery. *Archives of Internal Medicine* 1996, **156**(8):851-6. *(Guideline Ref ID: LEVINE1996)*

332. Levine MN, Hirsh J, Gent M, Turpie AG, Leclerc J, Powers PJ *et al*. Prevention of deep vein thrombosis after elective hip surgery. A randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Annals of Internal Medicine* 1991, **114**(7):545-51. *(Guideline Ref ID: LEVINE1991)*

333. Leyvraz P, Bachmann F, Bohnet J, Breyer HG, Estoppey D, Haas S *et al*. Thromboembolic prophylaxis in total hip replacement: a comparison between the low molecular weight heparinoid Lomoparan and heparin-dihydroergotamine. *British Journal of Surgery* 1992, **79**(9):911-4. *(Guideline Ref ID: LEYVRAZ1992)*

334. Lieberman JR, Geerts WH. Prevention of venous thromboembolism after total hip and knee arthroplasty. *Journal of Bone and Joint Surgery American Volume* 1994, **76**(8):1239-50. *(Guideline Ref ID: LIEBERMAN1994)*

335. Limmer J, Ellbruck D, Muller H, Eisele E, Rist J, Schutze F *et al*. Prospective randomized clinical study in general surgery comparing a new low molecular weight heparin with unfractionated heparin in the prevention of thrombosis. *Clinical Investigator* 1994, **72**(11):913-9. *(Guideline Ref ID: LIMMER1994)*

336. Lindstrom B, Holmdahl C, Jonsson O, Korsan-Bengtsen K, Lindberg S, Petrusson B *et al*. Prediction and prophylaxis of postoperative thromboembolism--a comparison between peroperative calf muscle stimulation with groups of impulses and dextran 40. *British*

*Journal of Surgery* 1982, **69**(11):633-7. *(Guideline Ref ID: LINDSTROM1982)*

337. Lloyd A, Aitken JA, Hoffmeyer UKO, Kelso EJ, Wakerly EC, Barber ND. Economic evaluation of the use of nadroparin calcium in the prophylaxis of deep vein thrombosis and pulmonary embolism in surgical patients in Italy. *Pharmacoeconomics* 1997, **12**(4):475-85. *(Guideline Ref ID: LLOYD1997)*

338. Loew D, Bruecke P, Simma W. Acetylsalicylic acid, low dose heparin, and a combination of both substances in the prevention of postoperative thromboembolism: a double blind study. *Thrombosis Research* 1977, **11**(1):81-6. *(Guideline Ref ID: LOEW1977)*

339. Lotke PA, Palevsky H, Keenan AM, Meranze S, Steinberg ME, Ecker ML *et al*. Aspirin and warfarin for thromboembolic disease after total joint arthroplasty. *Clinical Orthopaedics and Related Research* 1996,(324):251-8. *(Guideline Ref ID: LOTKE1996)*

340. Lowe LW. The role of anticoagulants in hip surgery. In: McKibbin B, ed. *Recent advances in orthopaedics. No. 3*, 1979. pp 31-55. Edinburgh: Churchill Livingstone. *(Guideline Reference ID: Ref ID: LOWE1979)*

341. Lowe LW. Venous thrombosis and embolism. *Journal of Bone and Joint Surgery British Volume* 1981, **63**(2):155-67. *(Guideline Ref ID: LOWE1981)*

342. Lumley T. Network meta-analysis for indirect treatment comparisons. *Statistics in Medicine* 2002, **21**(16):2313-24. *(Guideline Ref ID: LUMLEY2002)*

343. Lundkvist J, Bergqvist D, Jonsson B. Cost-effectiveness of fondaparinux vs. enoxaparin as venous thromboembolism prophylaxis in Sweden. *European Journal of Health Economics* 2003, **4**(4):254-62. *(Guideline Ref ID: LUNDKVIST2003)*

344. MacCallum PK, Thomson JM, Poller L. Effects of fixed minidose warfarin on coagulation and fibrinolysis following major gynaecological surgery. *Thrombosis and Haemostasis* 1990, **64**(4):511-5. *(Guideline Ref ID: MACCALLUM1990)*

345. Macdonald RL, Amidei C, Baron J, Weir B, Brown F, Erickson RK *et al*. Randomized, pilot study of intermittent pneumatic compression devices plus dalteparin versus intermittent pneumatic compression devices plus heparin for prevention of venous thromboembolism in patients undergoing craniotomy. *Surgical Neurology* 2003, **59**(5):363-72. *(Guideline Ref ID: MACDONALD2003)*

346. MacIntyre IMC, Vasilescu C, Jones DRB. Heparin versus dextran in the prevention of deep-vein thrombosis. A multi-unit controlled trial. *The Lancet* 1974, **2**(7873):118-20. *(Guideline Ref ID: MACINTYRE1974)*

347. Mamdani MM, Weingarten CM, Stevenson JG. Thromboembolic prophylaxis in moderate-risk patients undergoing elective abdominal surgery:decision and cost-effectiveness analyses (Structured abstract). *Pharmacotherapy* 1996, **16**(6):1111-27. *(Guideline Ref ID: MAMDANI1996)*

348. Manganelli D, Pazzagli M, Mazzantini D, Punzi G, Manca M, Vignali C *et al*. Prolonged prophylaxis with unfractioned heparin is effective to reduce delayed deep vein thrombosis in total hip replacement. *Respiration* 1998, **65**(5):369-74. *(Guideline Ref ID: MANGANELLI1998A)*

349. Mannucci PM, Citterio LE, Panajotopoulos N. Low-dose heparin and deep-vein thrombosis after total hip replacement. *Thrombosis and Haemostasis* 1976, **36**(1):157-64. *(Guideline Ref ID: MANNUCCI1976)*

350. Marassi A, Balzano G, Mari G, D'Angelo SV, Della VP, Di C, V *et al*. Prevention of postoperative deep vein thrombosis in cancer patients. A randomized trial with low molecular weight heparin (CY 216). *International Surgery* 1993, **78**(2):166-70. *(Guideline Ref ID: MARASSI1993)*

351. Marchetti M, Liberato NL, Ruperto N, Barosi G. Long-term cost-effectiveness of low molecular weight heparin versus unfractionated heparin for the prophylaxis of venous thromboembolism in elective hip replacement. *Haematologica* 1999, **84**(8):730-7. *(Guideline Ref ID: MARCHETTI1999)*

352. Marchetti V, Beati C, Pogliani EM, Vincre G. (Low-dose calcium-heparin prophylaxis in thoracic surgery. Bleeding, changes in coagulation and fibrinolysis). *Minerva Medica* 1983, **74**(28-29):1745-8. *(Guideline Ref ID: MARCHETTI1983)*

353. Marsh N. Fibrinolysis. Chichester: John Wiley & Sons, 1981.*(Guideline Ref ID: MARSH1981)*

354. Martino MA, Borges E, Williamson E, Siegfried S, Cantor AB, Lancaster J *et al*. Pulmonary embolism after major abdominal surgery in gynecologic oncology. *Obstetrics and Gynecology* 2006, **107**(3):666-71. *(Guideline Ref ID: MARTINO2006)*

355. Mätzsch T, Bergqvist D, Fredin H, Hedner U, Lindhagen A, Nistor L. Comparison of the thromboprophylactic effect of a low molecular weight heparin versus dextran in total hip replacement. *Thrombotic and Haemorrhagic Disorders* 1991, **3**(1):25-9. *(Guideline Ref ID: MATZSCH1991)*

356. Maxwell GL, Myers ER, Clarke-Pearson DL. Cost-effectiveness of deep venous thrombosis prophylaxis in gynecologic oncology surgery (Structured abstract). *Obstetrics and Gynecology* 2000, **95**(2):206-14. *(Guideline Ref ID: MAXWELL2000)*

357. Maxwell GL, Synan I, Dodge R, Carroll B, Clarke-Pearson DL. Pneumatic compression versus low molecular weight heparin in gynecologic oncology surgery: a randomized trial. *Obstetrics and Gynecology* 2001, **98**(6):989-95. *(Guideline Ref ID: MAXWELL2001)*

358. Mayo ME, Halil T, Browse NL. The incidence of deep vein thrombosis after prostatectomy. *British Journal of Urology* 1971, **43**(6):738-42. *(Guideline Ref ID: MAYO1971)*

359. McBride JA, Turpie AG, Kraus V, Hilz C. Failure of aspirin and dipyridamole to influence the incidence of leg scan detected venous thrombosis after elective hip surgery. *Thrombosis et Diathesis Haemorrhagica* 1975, **34**(2):564. *(Guideline Ref ID: MCBRIDE1975)*

360. McCarthy TG, McQueen J, Johnstone FD. A comparison of low dose subcutaneous heparin and intravenous dextran 70 in the prophylaxis of deep venous thrombosis after gynaecological surgery. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1974, **81**(6):486-91. *(Guideline Ref ID: MCCARTHY1974)*

361. McInnes J, Larson MG, Daltroy LH, Brown T, Fossel AH, Eaton HM *et al*. A controlled evaluation of continuous passive motion in patients undergoing total knee arthroplasty. *JAMA* 1992, **268**(11):1423-8. *(Guideline Ref ID: MCINNES1992)*

362. McKenna R, Galante J, Bachmann F, Wallace DL, Kaushal PS, Meredith P. Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. *BMJ* 1980, **280**(6213):514-7. *(Guideline Ref ID: MCKENNA1980)*

363. McKenzie PJ, Wishart HY, Gray I, Smith G. Effects of anaesthetic technique on deep vein thrombosis. A comparison of subarachnoid and general anaesthesia. *British Journal of Anaesthesia* 1985, **57**(9):853-7. *(Guideline Ref ID: MCKENZIE1985)*

364. McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM *et al*. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial. *Annals of Surgery* 2001, **233**(3):438-44. *(Guideline Ref ID: MCLEOD2001)*

365. McPherson K, Metcalfe MA, Herbert A, Maresh M, Casbard A, Hargreaves J *et al*. Severe complications of hysterectomy: the VALUE study. *BJOG* 2004, **111**(7):688-94. *(Guideline Ref ID: MCPHERSON2004)*

366. Mellbring G, Palmér K. Prophylaxis of deep vein thrombosis after major abdominal surgery. Comparison between dihydroergotamine-heparin and intermittent pneumatic calf compression and evaluation of added graduated static compression. *Acta Chirurgica Scandinavica* 1986, **152)**:597-600. *(Guideline Ref ID: MELLBRING1986)*

367. Melon E, Keravel Y, Gaston A, Huet Y, Combes S, NEURONOX Group. Deep venous thrombosis prophylaxis by low molecular weight heparin in neurosurgical patients [abstract]. *Anesthesiology* 1987, **75**:A214. *(Guideline Ref ID: MELON1987)*

368. Menzin J, Colditz GA, Regan MM, Richner RE, Oster G. Cost-effectiveness of enoxaparin vs low-dose warfarin in the prevention of deep-vein thrombosis after total hip replacement surgery. *Archives of Internal Medicine* 1995, **155**(7):757-64. *(Guideline Ref ID: MENZIN1995)*

369. Michot M, Conen D, Holtz D, Erni D, Zumstein MD, Ruflin GB *et al*. Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: A randomized trial of prophylaxis with low-molecular weight heparin. *Arthroscopy* 2002, **18**(3):257-63. *(Guideline Ref ID: MICHOT2002A)*

370. Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2002, **136**(9):680-90. *(Guideline Ref ID: MILLER2002)*

371. Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S *et al*. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA*

2006, **296**(6):679-90. *(Guideline Ref ID: MILLS2006)*

372. Mingus ML. Recovery advantages of regional anesthesia compared with general anesthesia: adult patients. *J Clin Anesth* 1995, **7**(7):628-33. *(Guideline Ref ID: MINGUS1995)*

373. Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *British Journal of Surgery* 2001, **88**(7):913-30. *(Guideline Ref ID: MISMETTI2001)*

374. Mismetti P, Laporte S, Zufferey P, Epinat M, Decousus H, Cucherat M. Prevention of venous thromboembolism in orthopedic surgery with vitamin K antagonists: a meta-analysis. *Journal of Thrombosis and Haemostasis : JTH* 2004, **2**(7):1058-70. *(Guideline Ref ID: MISMETTI2004)*

375. Mitchell D, Friedman RJ, Baker JD, III, Cooke JE, Darcy MD, Miller MC, III. Prevention of thromboembolic disease following total knee arthroplasty. Epidural versus general anesthesia. *Clinical Orthopaedics and Related Research* 1991,(269):109-12. *(Guideline Ref ID: MITCHELL1991)*

376. Modig J. The role of lumbar epidural anaesthesia as antithrombotic prophylaxis in total hip replacement. *Acta Chirurgica Scandinavica* 1985, **151**(7):589-94. *(Guideline Ref ID: MODIG1985)*

377. Modig J, Hjelmstedt A, Sahlstedt B, Maripuu E. Comparative influences of epidural and general anaesthesia on deep venous thrombosis and pulmonary embolism after total hip replacement. *Acta Chirurgica Scandinavica* 1981, **147**(2):125-30. *(Guideline Ref ID: MODIG1981)*

378. Mol EM, Egberts TCG. Prophylaxis for venous thromboembolism in hip fracture surgery. *Pharmacoeconomics* 1994, **5**(1):48-55. *(Guideline Ref ID: MOL1994)*

379. Monreal M, Lafoz E, Navarro A, Granero X, Caja V, Caceres E *et al*. A prospective double-blind trial of a low molecular weight heparin once daily compared with conventional low-dose heparin three times daily to prevent pulmonary embolism and venous thrombosis in patients with hip fracture. *Journal of Trauma* 1989, **29**(6):873-5. *(Guideline Ref ID: MONREAL1989A)*

380. Monreal M, Lafoz E, Roca J, Granero X, Soler J, Salazar X *et al*. Platelet count, antiplatelet therapy and pulmonary embolism -- a prospective study in patients with hip surgery. *Thrombosis and Haemostasis* 1995, **73**(3):380-5. *(Guideline Ref ID: MONREAL1995)*

381. Moreano EH, Hutchison JL, McCulloch TM, Graham SM, Funk GF, Hoffman HT. Incidence of deep venous thrombosis and pulmonary embolism in otolaryngology-head and neck surgery. *Otolaryngology - Head & Neck Surgery* 1998, **118**(6):777-84. *(Guideline Ref ID: MOREANO1998)*

382. Morris GK, Henry A-PJ, Preston BJ. Prevention of deep vein thrombosis by low dose heparin in patients undergoing total hip replacement. *The Lancet* 1974, **2**(7884):797-9. *(Guideline Ref ID: MORRIS1974)*

383. Morris GK, Mitchell JR. Warfarin sodium in prevention of deep venous thrombosis and pulmonary embolism in patients with fractured neck of femur. *The Lancet* 1976, **2**(7991):869-72. *(Guideline Ref ID: MORRIS1976)*

384. Morris GK, Mitchell JR. Preventing venous thromboembolism in elderly patients with hip fractures: studies of low-dose heparin, dipyridamole, aspirin, and flurbiprofen. *British Medical Journal* 1977, **1**(6060):535-7. *(Guideline Ref ID: MORRIS1977)*

385. Moskovitz PA, Ellenberg SS, Feffer HL, Kenmore P, I, Neviaser RJ, Rubin BE *et al*. Low-dose heparin for prevention of venous thromboembolism in total hip arthroplasty and surgical repair of hip fractures. *Journal of Bone and Joint Surgery* 1978, **60**(8):1065-70. *(Guideline Ref ID: MOSKOVITZ1978)*

386. Muntz J, Scott DA, Lloyd A, Egger M. Major bleeding rates after prophylaxis against venous thromboembolism: systematic review, meta-analysis, and cost implications. *International Journal of Technology Assessment in Health Care* 2004, **20**(4):405-14. *(Guideline Ref ID: MUNTZ2004)*

387. Myhre HO, Holen A. (Thrombosis prophylaxis. Dextran or warfarin-sodium? A controlled clinical study). *Nordisk Medicin* 1969, **82**(49):1534-8. *(Guideline Ref ID: MYHRE1969)*

388. National Institute for Health and Clinical Excellence. (2006) Obesity - guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. London: National Institute for Health and Clinical Excellence. *(Guideline Ref ID: NICE2006A)*

389. National Institute for Health and Clinical Excellence. (2006) The guidelines manual.

London: National Institute for Health and Clinical Excellence. *(Guideline Ref ID: NICE2006)*

390. National Joint Registry. (2006) National joint registry for England and Wales 3rd annual clinical report. Hemel Hempstead: Northgate Information Solutions Ltd. *(Guideline Ref ID: NJR2006A)*

391. Nerurkar J, Wade WE, Martin BC. Cost/death averted with venous thromboembolism prophylaxis in patients undergoing total knee replacement or knee arthroplasty. *Pharmacotherapy* 2002, **22**(8):990-1000. *(Guideline Ref ID: NERURKAR2002)*

392. NHS Prescription Pricing Authority. Electronic drug tariff http://www.ppa.org.uk/ppa/edt_intro.htm *(Guideline Ref ID: PPA2006)*

393. NHS Purchasing and Supplies Agency. NHS-eCat http://www.pasa.doh.gov.uk/ecat/ *(Guideline Ref ID: PASA2006)*

394. NHS Scotland. (2006) Scottish arthroplasty project annual report 2006. Edinburgh: NHS Scotland. *(Guideline Ref ID: NHSSCOTLAND2006)*

395. Nicolaides AN, Bergqvist D, Hull RD. Prevention of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). *International Angiology* 1997, **16**(1):3-38. *(Guideline Ref ID: ANON1997)*

396. Nicolaides AN, Dupont PA, Desai S, Lewis JD, Douglas JN, Dodsworth H *et al*. Small doses of subcutaneous sodium heparin in preventing deep venous thrombosis after major surgery. *The Lancet* 1972, **2**(7783):890-3. *(Guideline Ref ID: NICOLAIDES1972)*

397. Nicolaides AN, Miles C, Hoare M, Jury P, Helmis E, Venniker R. Intermittent sequential pneumatic compression of the legs and thromboembolism-deterrent stockings in the prevention of postoperative deep venous thrombosis. *Surgery* 1983, **94**(1):21-5. *(Guideline Ref ID: NICOLAIDES1983)*

398. Nielsen PT, Jørgensen LN, Albrecht-Beste E., Leffers AM, Rasmussen LS. Lower thrombosis risk with epidural blockade in knee arthroplasty. *Acta Orthopaedica Scandinavica* 1990, **61**(1):29-31. *(Guideline Ref ID: NIELSEN1990)*

399. Norgren L, Toksvig-Larsen S., Magyar G, Lindstrand A, Albrechtsson U. Prevention of deep vein thrombosis in knee arthroplasty. Preliminary results from a randomized controlled study of low molecular weight heparin vs foot pump compression. *International Angiology* 1998, **17**(2):93-6. *(Guideline Ref ID: NORGREN1998)*

400. Nurmohamed MT, van Riel AM, Henkens CM, Koopman MM, Que GT, d'Azemar P *et al*. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. *Thrombosis and Haemostasis* 1996, **75**(2):233-8. *(Guideline Ref ID: NURMOHAMED1996)*

401. Nurmohamed MT, Verhaeghe R, Haas S, Iriarte JA, Vogel G, van Rij AM *et al*. A comparative trial of a low molecular weight heparin (enoxaparin) versus standard heparin for the prophylaxis of postoperative deep vein thrombosis in general surgery. *American Journal of Surgery* 1995, **169**(6):567-71. *(Guideline Ref ID: NURMOHAMED1995A)*

402. O'Brien BJ, Anderson DR, Goeree R. Cost-effectiveness of enoxaparin versus warfarin prophylaxis against deep-vein thrombosis after total hip replacement. *Canadian Medical Association Journal* 1994, **150**(7):1083-90. *(Guideline Ref ID: OBRIEN1994)*

403. O'Meara JJ, III, McNutt RA, Evans AT, Moore SW, Downs SM. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. *New England Journal of Medicine* 1994, **330**(26):1864-9. *(Guideline Ref ID: OMEARA1994)*

404. O'Sullivan EF, Renney JT. Antiplatelet drugs in the prevention of postoperative deep vein thrombosis. In: *Proceedings of III Congress of International Society for Thrombosis and Haemostasis (Washington)*, 1972. p 438. *(Guideline Reference ID: Ref ID: OSULLIVAN1972)*

405. Ockelford PA, Patterson J, Johns AS. A double-blind randomized placebo controlled trial of thromboprophylaxis in major elective general surgery using once daily injections of a low molecular weight heparin fragment (Fragmin). *Thrombosis and Haemostasis* 1989, **62**(4):1046-9. *(Guideline Ref ID: OCKELFORD1989)*

406. Oertli D, Hess P, Durig M, Laffer U, Fridrich R, Jaeger K *et al*. Prevention of deep vein thrombosis in patients with hip fractures: low molecular weight heparin versus dextran. *World Journal of Surgery* 1992, **16**(5):980-4. *(Guideline Ref ID: OERTLI1992)*

407. Ohlund C, Fransson SG, Starck SA. Calf compression for prevention of

thromboembolism following hip surgery. *Acta Orthopaedica Scandinavica* 1983, **54**(6):896-9. *(Guideline Ref ID: OHLUND1983)*

408. Onarheim H, Lund T, Heimdal A, Arnesjo B. A low molecular weight heparin (KABI 2165) for prophylaxis of postoperative deep venous thrombosis. *Acta Chirurgica Scandinavica* 1986, **152**:593-6. *(Guideline Ref ID: ONARHEIM1986)*

409. Oostenbrink JB, Tangelder MJ, Busschbach JJ, van Hout BA, Buskens E, Algra A *et al.* Cost-effectiveness of oral anticoagulants versus aspirin in patients after infrainguinal bypass grafting surgery. *Journal of Vascular Surgery* 2001, **34**(2):254-62. *(Guideline Ref ID: OOSTENBRINK2001)*

410. Oster G, Tuden RL, Colditz GA. A cost-effectiveness analysis of prophylaxis against deep-vein thrombosis in major orthopedic surgery. *JAMA* 1987, **257**(2):203-8. *(Guideline Ref ID: OSTER1987A)*

411. Oster G, Tuden RL, Colditz GA. Prevention of venous thromboembolism after general surgery. Cost-effectiveness analysis of alternative approaches to prophylaxis. *American Journal of Medicine* 1987, **82**(5):889-99. *(Guideline Ref ID: OSTER1987)*

412. Paiement GD, Wessinger SJ, Walter AC, Harris WH. Low dose warfarin versus external pneumatic compression against venous thromboembolism following total hip replacement. *Journal of Arthroplasty* 1987, **2**(1):23-6. *(Guideline Ref ID: PAIEMENT1987)*

413. Palareti G, Borghi B, Coccheri S, Leali N, Golfieri R, Montebugnoli M *et al.* Postoperative versus preoperative initiation of deep-vein thrombosis prophylaxis with a low-molecular-weight heparin (Nadroparin) in elective hip replacement. *Clinical and Applied Thrombosis/Hemostasis* 1996, **2**(1):18-24. *(Guideline Ref ID: PALARETI1996)*

414. Parodi JC, Grandi A, Font E, Rotondaro D, Iorio J, Manrique J. El dipiridamol y el acido acetilsalicilico en la profilaxis de las trombosis venosas postoperatorias de los miembros inferiores. *Dia Medico* 1973, **45**:92-3. *(Guideline Ref ID: PARODI1973)*

415. Perhoniemi V, Vuorinen J, Myllynen P, Kivioja A, Lindevall K. The effect of enoxaparin in prevention of deep venous thrombosis in hip and knee surgery--a comparison with the dihydroergotamine-heparin combination. *Annales Chirurgiae et Gynaecologiae* 1996, **85**(4):359-63. *(Guideline Ref ID: PERHONIEMI1996)*

416. Pezzuoli G, Neri Serneri GG, Settembrini P, Coggi G, Olivari N, Buzzetti G *et al.* Prophylaxis of fatal pulmonary embolism in general surgery using low-molecular weight heparin Cy 216: a multicentre, double-blind, randomized, controlled, clinical trial versus placebo (STEP). STEP-Study Group. *International Surgery* 1989, **74**(4):205-10. *(Guideline Ref ID: PEZZUOLI1989)*

417. Pezzuoli G, Neri-Serneri GG, Settembrini PG, Coggi G, Olivari N, Negri G *et al.* Effectiveness and safety of the low-molecular-weight heparin CY 216 in the prevention of fatal pulmonary embolism and thromboembolic death in general surgery. A multicentre, double-blind, randomized, controlled clinical trial versus placebo (STEP). STEP Study Group. *Haemostasis* 1990, **20 Suppl 1**:193-204. *(Guideline Ref ID: PEZZUOLI1990)*

418. Phillips CB, Barrett JA, Losina E, Mahomed NN, Lingard EA, Guadagnoli E *et al.* Incidence rates of dislocation, pulmonary embolism, and deep infection during the first six months after elective total hip replacement. *Journal of Bone & Joint Surgery - American Volume* 2003, **85-A**(1):20-6. *(Guideline Ref ID: PHILLIPS2003)*

419. Pinto DJ. Controlled trial of an anticoagulant (warfarin sodium) in the prevention of venous thrombosis following hip surgery. *British Journal of Surgery* 1970, **57**(5):349-52. *(Guideline Ref ID: PINTO1970)*

420. Pitto RP, Hamer H, Heiss-Dunlop W, Kuehle J. Mechanical prophylaxis of deep-vein thrombosis after total hip replacement a randomised clinical trial. *Journal of Bone and Joint Surgery British Volume* 2004, **86**(5):639-42. *(Guideline Ref ID: PITTO2004)*

421. Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *The Lancet* 1996, **348**(9022):224-8. *(Guideline Ref ID: PLANES1996B)*

422. Planès A, Vochelle N, Fagola M, Bellaud M, Feret J, Salzard C *et al.* Once-daily dosing of enoxaparin (a low molecular weight heparin) in prevention of deep vein thrombosis after total hip replacement. *Acta Chirurgica Scandinavica Supplementum* 1990, **556**:108-15. *(Guideline Ref ID: PLANÈS1990A)*

423. Plante J, Boneu B, Vaysse C. Dipyridamole-aspirin versus low doses of heparin in the prophylaxis of deep venous thrombosis in abdominal surgery. *Thrombosis Research* 1979,

**14**(2-3):399-403. *(Guideline Ref ID: PLANTE1979)*

424. Poikolainen E, Hendolin H. Effects of lumbar epidural analgesia and general anaesthesia on flow velocity in the femoral vein and postoperative deep vein thrombosis. *Acta Chirurgica Scandinavica* 1983, **149**(4):361-4. *(Guideline Ref ID: POIKOLAINEN1983)*

425. Poller L, McKernan A, Thomson JM, Elstein M, Hirsch PJ, Jones JB. Fixed minidose warfarin: a new approach to prophylaxis against venous thrombosis after major surgery. *BMJ* 1987, **295**(6609):1309-12. *(Guideline Ref ID: POLLER1987)*

426. Poller L, Thomson JM, MacCallum PK, Nicholson DA, Weighill FJ, Lemon JG. Minidose warfarin and failure to prevent deep vein thrombosis after joint replacement surgery despite inhibiting the postoperative rise in plasminogen activator inhibitor activity. *Clinical and Applied Thrombosis/Hemostasis* 1995, **1**:267-73. *(Guideline Ref ID: POLLER1995)*

427. Porteous MJ, Nicholson EA, Morris LT, James R, Negus D. Thigh length versus knee length stockings in the prevention of deep vein thrombosis. *British Journal of Surgery* 1989, **76**(3):296-7. *(Guideline Ref ID: PORTEOUS1989)*

428. Powers PJ, Gent M, Jay RM, Julian DH, Turpie AG, Levine M *et al*. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. *Archives of Internal Medicine* 1989, **149**(4):771-4. *(Guideline Ref ID: POWERS1989)*

429. Prandoni P, Bruchi O, Sabbion P, Tanduo C, Scudeller A, Sardella C *et al*. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. *Archives of Internal Medicine* 2002, **162**(17):1966-71. *(Guideline Ref ID: PRANDONI2002)*

430. Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A *et al*. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. *Haematologica* 1997, **82**(4):423-8. *(Guideline Ref ID: PRANDONI1997)*

431. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *The Lancet* 2000, **355**(9212):1295-302. *(Guideline Ref ID: PEP2000)*

432. R Development Core Team. A language and environment for statistical computing. 2005. *(Guideline Reference ID: R2005)*

433. Ramaswami G, Nicolaides AN. The cost-effectiveness of mechanical forms of DVT prophylaxis in general surgery (Structured abstract). *International Angiology* 1996, **15**(3 Suppl 1):21-6. *(Guideline Ref ID: RAMASWAMI1996)*

434. Ramos R, Salem B, I, De Pawlikowski MP, Coordes C, Eisenberg S, Leidenfrost R. The efficacy of pneumatic compression stockings in the prevention of pulmonary embolism after cardiac surgery. *Chest* 1996, **109**(1):82-5. *(Guideline Ref ID: RAMOS1996)*

435. Rasmussen A, Hansen PT, Lindholt J, Poulsen TD, Toftdahl DB, Gram J *et al*. Venous thrombosis after abdominal surgery. A comparison between subcutaneous heparin and antithrombotic stockings, or both. *Journal of Medicine* 1988, **19**(3-4):193-201. *(Guideline Ref ID: RASMUSSEN1988)*

436. Rasmussen MS. Preventing thromboembolic complications in cancer patients after surgery: a role for prolonged thromboprophylaxis. *Cancer Treatment Reviews* 2002, **28**(3):141-4. *(Guideline Ref ID: RASMUSSEN2002)*

437. Reeves P, Cooke J, Lloyd A, Hutchings A. An economic evaluation of the costs and benefits of heparin rationalisation in a hospital pharmacy. *Pharmacy World and Science* 2004, **26**(3):160-8. *(Guideline Ref ID: REEVES2004)*

438. Reilmann H, Bosch U, Creutzig H, Oetting G, Fuchs I, Tscherne H. Thromboseprophylaxe mit niedermolekularem Heparin plus Dihydroergotamin be Operationen an den unteren Extremitäten. *Perfusion* 1989,230-4. *(Guideline Ref ID: REILMANN1989)*

439. Renney JT, O'Sullivan EF, Burke PF. Prevention of postoperative deep vein thrombosis with dipyridamole and aspirin. *BMJ* 1976, **1**(6016):992-4. *(Guideline Ref ID: RENNEY1976)*

440. Ribaudo JM, Hoellrich RG, McKinnon WM, Shuler SE. Evaluation of mini-dose heparin administration as a prophylaxis against postoperative pulmonary embolism: a prospective double-blind study. *American Surgeon* 1975, **41**(5):289-95. *(Guideline Ref ID: RIBAUDO1975A)*

441. Ribaudo JM, Hoellrich RG, McKinnon W-MP, Shuler SE. Evaluation of mini dose heparin administration as a prophylaxis against postoperative pulmonary embolization: a

prospective double blind study. *Review of Surgery* 1975, **32**(4):297-9. *(Guideline Ref ID: RIBAUDO1975)*

442. Roberts VC, Cotton LT. Failure of low-dose heparin to improve efficacy of peroperative intermittent calf compression in preventing postoperative deep vein thrombosis. *British Medical Journal* 1975, **3**(5981):458-60. *(Guideline Ref ID: ROBERTS1975)*

443. Robertson KA, Bertot AJ, Wolfe MW, Barrack RL. Patient compliance and satisfaction with mechanical devices for preventing deep venous thrombosis after joint replacement. *Journal of the Southern Orthopaedic Association* 2000, **9**(3):182-6. *(Guideline Ref ID: ROBERTSON2000)*

444. Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R *et al*. Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis. *Health Technology Assessment* 2005, **9**(49). *(Guideline Ref ID: RODERICK2005)*

445. Rodrigo P, Alvarez M, Olmos M, Santos I, Velasco A. Deep vein thrombosis following knee replacement:The role of thrombosis prophylaxis combined with epidural anesthesia. *Haemostasis* 1994, **24**(Suppl 1):235. *(Guideline Ref ID: RODRIGO1994)*

446. Rokito SE, Schwartz MC, Neuwirth MG. Deep vein thrombosis after major reconstructive spinal surgery. *Spine* 1996, **21**(7):853-8. *(Guideline Ref ID: ROKITO1996)*

447. Rosengarten DS, Laird J. The effect of leg elevation on the incidence of deep-vein thrombosis after operation. *British Journal of Surgery* 1971, **58**(3):182-4. *(Guideline Ref ID: ROSENGARTEN1971A)*

448. Rosengarten DS, Laird J, Jeyasingh K, Martin P. The failure of compression stockings (Tubigrip) to prevent deep venous thrombosis after operation. *British Journal of Surgery* 1970, **57**(4):296-9. *(Guideline Ref ID: ROSENGARTEN1970)*

449. Royal College of Obstetricians and Gynaecologists. Hormone replacement therapy and venous thromboembolism http://www.rcog.org.uk/resources/Public/pdf/HRT_Venous_Thromboembolism_no19.pdf [accessed 1-3-0006]. *(Guideline Ref ID: RCOG2004)*

450. Royal College of Obstetricians and Gynaecologists. Venous Thromboembolism and Hormonal Contraception (Guideline No. 40) http://www.rcog.org.uk/resources/Public/pdf/VTE_hormonal_contraception.pdf [accessed 1-3-0006]. *(Guideline Ref ID: RCOG2004A)*

451. Ryan MG, Westrich GH, Potter HG, Sharrock N, Maun LM, Macaulay W *et al*. Effect of mechanical compression on the prevalence of proximal deep venous thrombosis as assessed by magnetic resonance venography. *Journal of Bone and Joint Surgery* 2002, **84-A**(11):1998-2004. *(Guideline Ref ID: RYAN2002)*

452. Saarinen J, Sisto T, Laurikka J, Salenius JP, Tarkka M. The incidence of postoperative deep vein thrombosis in vascular procedures. FINNVASC Study Group. *Vasa* 1995, **24**(2):126-9. *(Guideline Ref ID: SAARINEN1995)*

453. Sagar S. Heparin prophylaxis against fatal postoperative pulmonary embolism. *British Medical Journal* 1974, **2**(5911):153-5. *(Guideline Ref ID: SAGAR1974)*

454. Sagar S, Massey J, Sanderson JM. Low-dose heparin prophylaxis against fatal pulmonary embolism. *British Medical Journal* 1975, **4**(5991):257-9. *(Guideline Ref ID: SAGAR1975)*

455. Salcuni PF, Azzarone M, Palazzini E. A new low molecular weight heparin for deep vein thrombosis prevention: effectiveness in postoperative patients. *Current Therapeutic Research* 1988, **43**:824-31. *(Guideline Ref ID: SALCUNI1988)*

456. Salzman EW, Davies GC. Prophylaxis of venous thromboembolism. Analysis of cost effectiveness. *Annals of Surgery* 1980, **191**(2):207-18. *(Guideline Ref ID: SALZMAN1980A)*

457. Samama CM, Bastien O, Forestier F, Denninger M-H, Isetta C, Julliard J-M *et al*. Antiplatelet agents in the perioperative period : expert recommendations of the french society of anesthesiology and intensive care (sfar) 2001 – summary http://www.sfar.org/pdf/aapconfexp2.pdf *(Guideline Ref ID: SAMAMA2001)*

458. Samama CM, Clergue F, Barre J, Montefiore A, Ill P, Samii K. Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. Arar Study Group. *British Journal of Anaesthesia* 1997, **78**(6):660-5. *(Guideline Ref ID: SAMAMA1997)*

459. Samama M, Bernard P, Bonnardot JP, Combe-Tamzali S, Lanson Y, Tissot E. Low molecular weight heparin compared with unfractionated heparin in prevention of postoperative thrombosis. *British Journal of Surgery* 1988, **75**(2):128-31. *(Guideline Ref ID: SAMAMA1988)*

460. Samama M, Combe S. Prevention of thromboembolic disease in general surgery with enoxaparin (Clexane). *Acta Chirurgica Scandinavica* 1990, **156**(556):91-5. *(Guideline Ref ID: SAMAMA1990)*

461. Samama M, Combe-Tamzali S. Prevention of thromboembolic disease in general surgery with enoxaparin. *British Journal of Clinical Practice* 1989, **43 Suppl 65**:9-17. *(Guideline Ref ID: SAMAMA1989)*

462. Samama MM. Prevention of postoperative thromboembolism in general surgery with enoxaparin. *European Journal of Surgery Supplement* 1994,(571):31-3. *(Guideline Ref ID: SAMAMA1994)*

463. Samama MM, Dahl OE, Quinlan DJ, Mismetti P, Rosencher N. Quantification of risk factors for venous thromboembolism: a preliminary study for the development of a risk assessment tool. *Haematologica* 2003, **88**(12):1410-21. *(Guideline Ref ID: SAMAMA2003)*

464. Santori FS, Vitullo A, Stopponi M, Santori N, Ghera S. Prophylaxis against deep-vein thrombosis in total hip replacement. Comparison of heparin and foot impulse pump. *Journal of Bone and Joint Surgery British Volume* 1994, **76**(4):579-83. *(Guideline Ref ID: SANTORI1994)*

465. Sarasin FP, Bounameaux H. Antithrombotic strategy after total hip replacement: a cost-effectiveness analysis comparing prolonged oral anticoagulants with screening for deep vein thrombosis (Structured abstract). *Archives of Internal Medicine* 1996, **156**(15):1661-8. *(Guideline Ref ID: SARASIN1996A)*

466. Sarasin FP, Bounameaux H. Cost-effectiveness of prophylactic anticoagulation prolonged after hospital discharge following general surgery. *Archives of Surgery* 1996, **131**(7):694-7. *(Guideline Ref ID: SARASIN1996)*

467. Sarasin FP, Bounameaux H. Out of hospital antithrombotic prophylaxis after total hip replacement: low-molecular-weight heparin, warfarin, aspirin or nothing? *Thrombosis and Haemostasis* 2002, **87**(4):586-92. *(Guideline Ref ID: SARASIN2002)*

468. Sarasin FP, Eckman MH. Management and prevention of thromboembolic events in patients with cancer-related hypercoagulable states: a risky business. *Journal of General Internal Medicine* 1993, **8**(9):476-86. *(Guideline Ref ID: SARASIN1993)*

469. Sasahara AA, DiSerio FJ, Singer JM. Dihydroergotamine-heparin prophylaxis of postoperative deep vein thrombosis. A multicenter trial. *Journal of the American Medical Association* 1984, **251**(22):2960-6. *(Guideline Ref ID: SASAHARA1984)*

470. Sasahara AA, Koppenhagen K, Häring R, Welzel D, Wolf H. Low molecular weight heparin plus dihydroergotamine for prophylaxis of postoperative deep vein thrombosis. *British Journal of Surgery* 1986, **73**(9):697-700. *(Guideline Ref ID: SASAHARA1986)*

471. Sautter RD, Koch EL, Myers WO, Ray JR, III, Mazza JJ, Larson DE *et al*. Aspirin-sulfinpyrazone in prophylaxis of deep venous thrombosis in total hip replacement. *JAMA* 1983, **250**(19):2649-54. *(Guideline Ref ID: SAUTTER1983)*

472. Schielke DJ, Staib I, Wolf H, Mankel T. Prophylaxis of thromboembolism in abdominal surgery: effectiveness and tolerance of low molecular weight heparin in combination with dihydroergotamine. *Medizinische Welt* 1991, **42**:346-9. *(Guideline Ref ID: SCHIELKE1991)*

473. Schmitz-Huebner U, Bunte H, Freise G, Reers B, Ruschemeyer C, Scherer R *et al*. Clinical efficacy of low molecular weight heparin in postoperative thrombosis prophylaxis. *Klinische Wochenschrift* 1984, **62**(8):349-53. *(Guideline Ref ID: SCHMITZHUEBNER1984)*

474. Schondorf TH, Weber U. Prevention of deep vein thrombosis in orthopedic surgery with the combination of low dose heparin plus either dihydroergotamine or dextran. *Scandinavian Journal of Haematology Supplementum* 1980, **36**:126-40. *(Guideline Ref ID: SCHONDORF1980)*

475. Schreiber U, Hartung B. Postoperative thromboembolieprophylaxe bei patienten mit allgemeinchirurgischen operationen. *Zentralblatt fur Chirurgie* 1979, **104**(18):1214-20. *(Guideline Ref ID: SCHREIBER1979)*

476. Scottish Intercollegiate Guidelines Network. (2002) Prophylaxis of venous thromboembolism. Edinburgh: Scottish Intercollegiate Guidelines Network. *(Guideline Ref ID: SIGN2002)*

477. Scurr JH, Coleridge-Smith PD, Hasty JH. Regimen for improved effectiveness of intermittent pneumatic compression in deep venous thrombosis prophylaxis. *Surgery* 1987, **102**(5):816-20. *(Guideline Ref ID: SCURR1987)*

478. Scurr JH, Ibrahim SZ, Faber RG, Le Quesne LP. The efficacy of graduated compression stockings in the prevention of deep vein thrombosis. *British Journal of Surgery* 1977, **64**(5):371-3. *(Guideline Ref ID: SCURR1977)*

479. Scurr JH, Robbe IJ, Ellis H, Goldsmith HS. Simple mechanical method for decreasing the incidence of thromboembolism. *American Journal of Surgery* 1981, **141**(5):582-5. *(Guideline Ref ID: SCURR1981)*

480. Seagroatt V, Goldacre M. Measures of early postoperative mortality: beyond hospital fatality rates. *BMJ* 1994, **309**(6951):361-5. *(Guideline Ref ID: SEAGROATT1994)*

481. Sebeseri O, Kummer H, Zingg E. Controlled prevention of post-operative thrombosis in urological diseases with depot heparin. *European Urology* 1975, **1**(5):229-30. *(Guideline Ref ID: SEBESERI1975)*

482. Senaran H, Acaroglu E, Ozdemir HM, Atilla B. Enoxaparin and heparin comparison of deep vein thrombosis prophylaxis in total hip replacement patients. *Archives of Orthopaedic and Trauma Surgery* 2006, **126**(1):1-5. *(Guideline Ref ID: SENARAN2006)*

483. Shirai N. Study on prophylaxis of postoperative deep vein thrombosis. *Acta Scholae Medicinalis Universitatis in Gifu* 1985, **33**(6):1173-83. *(Guideline Ref ID: SHIRAI1985)*

484. Sigel B, Edelstein AL, Felix WR, Jr., Memhardt CR. Compression of the deep venous system of the lower leg during inactive recumbency. *Archives of Surgery* 1973, **106**(1):38-43. *(Guideline Ref ID: SIGEL1973)*

485. Silbersack Y, Taute BM, Hein W, Podhaisky H. Prevention of deep-vein thrombosis after total hip and knee replacement. Low-molecular-weight heparin in combination with intermittent pneumatic compression. *Journal of Bone and Joint Surgery British Volume* 2004, **86**(6):809-12. *(Guideline Ref ID: SILBERSACK2004)*

486. Sinclair J, Forbes CD, Prentice CR, Scott R. The incidence of deep vein thrombosis in prostatectomised patients following the administration of the fibrinolytic inhibitor, aminocaproic acid (EACA). *Urological Research* 1976, **4**(3):129-31. *(Guideline Ref ID: SINCLAIR1976)*

487. Siragusa S, Vicentini L, Carbone S, Barone M, Beltrametti C, Piovella F. Intermittent pneumatic leg compression (IPLC) and unfractionated heparin (UFH) in the prevention of post-operative deep vein thrombosis in hip surgery. *Blood* 1994, **84**(10 Suppl 1):70a. *(Guideline Ref ID: SIRAGUSA1994)*

488. Skillman JJ, Collins RE, Coe NP, Goldstein BS, Shapiro RM, Zervas NT *et al*. Prevention of deep vein thrombosis in neurosurgical patients: a controlled, randomized trial of external pneumatic compression boots. *Surgery* 1978, **83**(3):354-8. *(Guideline Ref ID: SKILLMAN1978)*

489. Smith RC, Elton RA, Orr JD, Hart AJ, Graham IF, Fuller GA *et al*. Dextran and intermittent pneumatic compression in prevention of postoperative deep vein thrombosis: multiunit trial. *BMJ* 1978, **1**(6118):952-4. *(Guideline Ref ID: SMITH1978)*

490. Sobolewski AP, Deshmukh RM, Brunson BL, McDevitt DT, VanWagenen TM, Lohr JM *et al*. Venous hemodynamic changes during laparoscopic cholecystectomy. *Journal of Laparoendoscopic Surgery* 1995, **5**(6):363-9. *(Guideline Ref ID: SOBOLEWSKI1995)*

491. Soderdahl DW, Henderson SR, Hansberry KL. A comparison of intermittent pneumatic compression of the calf and whole leg in preventing deep venous thrombosis in urological surgery. *Journal of Urology* 1997, **157**:1774-6. *(Guideline Ref ID: SODERDAHL1997)*

492. Sourmelis S, Patoulis G, Tzortzis G. Prevention of deep vein thrombosis with low molecular weight heparin in fractures of the hip [abstract]. *Journal of Bone and Joint Surgery British Volume* 1995, **77 Suppl 2**:173. *(Guideline Ref ID: SOURMELIS1995)*

493. Spahn G. Compliance with self-administration of heparin injections in outpatients. *European Journal of Trauma* 2002, **28**(2):104-9. *(Guideline Ref ID: SPAHN2002)*

494. Spebar MJ, Collins GJ, Jr., Rich NM, Kang IY, Clagett GP, Salander JM. Perioperative heparin prophylaxis of deep venous thrombosis in patients with peripheral vascular disease. *American Journal of Surgery* 1981, **142**(6):649-50. *(Guideline Ref ID: SPEBAR1981)*

495. Spiro TE, Johnson GJ, Christie MJ, Lyons RM, MacFarlane DE, Blasier RB *et al*. Efficacy and safety of enoxaparin to prevent deep venous thrombosis after hip replacement surgery. Enoxaparin Clinical Trial Group. *Annals of*

*Internal Medicine* 1994, **121**(2):81-9. *(Guideline Ref ID: SPIRO1994A)*

496. Spruill WJ, Wade WE, Leslie RB. A cost analysis of fondaparinux versus enoxaparin in total knee arthroplasty (Provisional record). *Journal of Therapeutics* 2004, **11**(1):3-8. *(Guideline Ref ID: SPRUILL2004)*

497. Spruill WJ, Wade WE, Leslie RB. Cost analysis of fondaparinux versus enoxaparin as venous thromboembolism prophylaxis in elective hip replacement surgery. *Blood coagulation & fibrinolysis* 2004, **15**(7):539-43. *(Guideline Ref ID: SPRUILL2004B)*

498. Stannard JP, Harris RM, Bucknell AL, Cossi A, Ward J, Arrington ED. Prophylaxis of deep venous thrombosis after total hip arthroplasty by using intermittent compression of the plantar venous plexus. *American Journal of Orthopedics* 1996, **25**(2):127-34. *(Guideline Ref ID: STANNARD1996)*

499. Stannard JP, Riley RS, McClenney MD, Lopez-Ben RR, Volgas DA, Alonso JE. Mechanical prophylaxis against deep-vein thrombosis after pelvic and acetabular fractures. *Journal of Bone and Joint Surgery* 2001, **83-A**(7):1047-51. *(Guideline Ref ID: STANNARD2001)*

500. Stephenson CBS, Wallace JC, Vaughan J, V. Dextran 70 in the prevention of post operative deep vein thrombosis with observations on pulmonary embolism: report on a pilot study. *New Zealand Medical Journal* 1973, **77**(492):302-5. *(Guideline Ref ID: STEPHENSON1973)*

501. Stone MH, Limb D, Campbell P, Stead D, Culleton G. A comparison of intermittent calf compression and enoxaparin for thromboprophylaxis in total hip replacement. A pilot study. *International Orthopaedics* 1996, **20**(6):367-9. *(Guideline Ref ID: STONE1996)*

502. Storti S, Crucitti P, Cina G. Risk factors and prevention of venous thromboembolism. *Rays* 1996, **21**(3):439-60. *(Guideline Ref ID: STORTI1996)*

503. Strand L, Bank-Mikkelsen OK, Lindewald H. Small heparin doses as prophylaxis against deep-vein thrombosis in major surgery. *Acta Chirurgica Scandinavica* 1975, **141**(7):624-7. *(Guideline Ref ID: STRAND1975)*

504. Stranks GJ, MacKenzie NA, Grover ML, Fail T. The A-V Impulse System reduces deep-vein thrombosis and swelling after hemiarthroplasty for hip fracture. *Journal of Bone and Joint Surgery British Volume* 1992, **74**(5):775-8. *(Guideline Ref ID: STRANKS1992)*

505. Sullivan SD, Davidson BL, Kahn SR, Muntz JE, Oster G, Raskob G. A cost-effectiveness analysis of fondaparinux sodium compared with enoxaparin sodium as prophylaxis against venous thromboembolism: use in patients undergoing major orthopaedic surgery. *Pharmacoeconomics* 2004, **22**(9):605-20. *(Guideline Ref ID: SULLIVAN2004)*

506. Sullivan SD, Kahn SR, Davidson BL, Borris L, Bossuyt P, Raskob G. Measuring the outcomes and pharmacoeconmics consequences of venous thromboembolism prophylaxis in major orthopaedic surgery. *Pharmacoeconomics* 2003, **21**(7):477-96. *(Guideline Ref ID: SULLIVAN2003)*

507. Sullivan SD, Kwong L, Nutescu E. Cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against venous thromboembolism in patients undergoing hip fracture surgery. *Value in Health* 2006, **9**(2):68-76. *(Guideline Ref ID: SULLIVAN2006)*

508. Svend-Hansen H, Bremerskov V, Gotrik J, Ostri P. Low-dose heparin in proximal femoral fractures. Failure to prevent deep-vein thrombosis. *Acta Orthopaedica Scandinavica* 1981, **52**(1):77-80. *(Guideline Ref ID: SVENDHANSEN1981)*

509. Swierstra BA, Stibbe J, Schouten HJ. Prevention of thrombosis after hip arthroplasty. A prospective study of preoperative oral anticoagulants. *Acta Orthopaedica Scandinavica* 1988, **59**(2):139-43. *(Guideline Ref ID: SWIERSTRA1988)*

510. Swierstra BA, van Oosterhout FJ, Ausema B, Bakker WH, van der Pompe WB, Schouten HJ. Oral anticoagulants and dextran for prevention of venous thrombosis in orthopaedics. *Acta Orthopaedica Scandinavica* 1984, **55**(3):251-3. *(Guideline Ref ID: SWIERSTRA1984)*

511. Szucs TD, Schramm W. The cost-effectiveness of low-molecular-weight heparin vs unfractionated heparin in general and orthopaedic surgery: an analysis for the German healthcare system. *Pharmacological Research* 1999, **40**(1):83-9. *(Guideline Ref ID: SZUCS1999)*

512. Taberner DA, Poller L, Burslem RW, Jones JB. Oral anticoagulants controlled by the British comparative thromboplastin versus low-dose heparin in prophylaxis of deep vein thrombosis. *BMJ* 1978, **1**(6108):272-4. *(Guideline Ref ID: TABERNER1978)*

513. The FOOD Trial Collaboration. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised

controlled trial. *The Lancet* 2005, **365**(9461):*755*-63. *(Guideline Ref ID: FOOD2005A)*

514. The German Hip Arthroplasty Trial (GHAT) Group. Prevention of deep vein thrombosis with low molecular-weight heparin in patients undergoing total hip replacement. A randomized trial. *Archives of Orthopaedic and Trauma Surgery* 1992, **111**(2):110-20. *(Guideline Ref ID: GHAT1992)*

515. The PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. *Circulation* 2005, **112**(3):416-22. *(Guideline Ref ID: PREPIC2005)*

516. Tincani E, Piccoli M, Turrini F, Crowther MA, Melotti G, Bondi M. Video laparoscopic surgery: is out-of-hospital thromboprophylaxis necessary? *Journal of Thrombosis and Haemostasis : JTH* 2005, **3**(2):216-20. *(Guideline Ref ID: TINCANI2005)*

517. Tørholm C, Broeng L, Jørgensen PS, Bjerregaard P, Josephsen L, Jørgensen PK *et al*. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. A placebo controlled study. *Journal of Bone and Joint Surgery British Volume* 1991, **73**(3):434-8. *(Guideline Ref ID: TØRHOLM1991)*

518. Törngren S. Prophylaxis of postoperative deep venous thrombosis. Studies on low-dose heparin, blood coagulation, infection as a risk factor and the half-life of fibrinogen in patients after gastrointestinal surgery. *Acta Chirurgica Scandinavica Supplementum* 1979,(495):1-69. *(Guideline Ref ID: TÖRNGREN1979)*

519. Torngren S. Low dose heparin and compression stockings in the prevention of postoperative deep venous thrombosis. *British Journal of Surgery* 1980, **67**(7):482-4. *(Guideline Ref ID: TORNGREN1980)*

520. Törngren S, Forsberg K. Concentrated or diluted heparin prophylaxis of postoperative deep venous thrombosis. *Acta Chirurgica Scandinavica* 1978, **144**(5):283-8. *(Guideline Ref ID: TÖRNGREN1978)*

521. Tsapogas MJ, Goussous H, Peabody RA, Karmody AM, Eckert C. Postoperative venous thrombosis and the effectiveness of prophylactic measures. *Archives of Surgery* 1971, **103**(5):561-7. *(Guideline Ref ID: TSAPOGAS1971)*

522. Turner GM, Cole SE, Brooks JH. The efficacy of graduated compression stockings in the prevention of deep vein thrombosis after major gynaecological surgery. *British Journal of Obstetrics and Gynaecology* 1984, **91**(6):588-91. *(Guideline Ref ID: TURNER1984)*

523. Turpie AG, Delmore T, Hirsh J, Hull R, Genton E, Hiscoe C *et al*. Prevention of venous thrombosis by intermittent sequential calf compression in patients with intracranial disease. *Thrombosis Research* 1979, **15**(5-6):611-6. *(Guideline Ref ID: TURPIE1979)*

524. Turpie AG, Gallus A, Beattie WS, Hirsh J. Prevention of venous thrombosis in patients with intracranial disease by intermittent pneumatic compression of the calf. *Neurology* 1977, **27**(5):435-8. *(Guideline Ref ID: TURPIE1977)*

525. Turpie AG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. *New England Journal of Medicine* 2001, **344**(9):619-25. *(Guideline Ref ID: TURPIE2001)*

526. Turpie AG, Hirsh J, Gent M, Julian D, Johnson J. Prevention of deep vein thrombosis in potential neurosurgical patients. A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Archives of Internal Medicine* 1989, **149**(3):679-81. *(Guideline Ref ID: TURPIE1989)*

527. Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ *et al*. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. *New England Journal of Medicine* 1986, **315**(15):925-9. *(Guideline Ref ID: TURPIE1986)*

528. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *The Lancet* 2002, **359**(9319):1721-6. *(Guideline Ref ID: TURPIE2002K)*

529. Urbanyi B, Spillner G, Schleinzer P. Prophylaxis against thromboembolism in vascular surgery. *Vascular Surgery* 1982, **16**:253-9. *(Guideline Ref ID: URBANYI1982)*

530. Valladares JB, Hankinson J. Incidence of lower extremity deep vein thrombosis in neurosurgical patients. *Neurosurgery* 1980, **6**(2):138-41. *(Guideline Ref ID: VALLADARES1980)*

531. Valle I, Sola G, Origone A. Controlled clinical study of the efficacy of a new low molecular weight heparin administered subcutaneously to prevent post-operative deep venous thrombosis. *Current Medical Research and Opinion* 1988, **11**(2):80-6. *(Guideline Ref ID: VALLE1988)*

532. Van Blerk D. Evaluating an intermittent compression system for thromboembolism prophylaxis. *Professional Nurse* 2004, **20**(4):48-9. *(Guideline Ref ID: VANBLERK2004)*

533. van Geloven F, Wittebol P, Sixma JJ. Comparison of postoperative coumarin, dextran 40 and subcutaneous heparin in the prevention of postoperative deep vein thrombosis. *Acta Medica Scandinavica* 1977, **202**(5):367-72. *(Guideline Ref ID: VANGELOVEN1977)*

534. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. *Health Economics* 1994, **3**(5):309-19. *(Guideline Ref ID: VANHOUT1994)*

535. Van Vroonhoven TJMV, Van Zijl J, Muller H. Low dose subcutaneous heparin versus oral anticoagulants in the prevention of postoperative deep venous thrombosis. A controlled clinical trial. *The Lancet* 1974, **1**(7854):375-8. *(Guideline Ref ID: VANVROONHOVEN1974)*

536. Vandendris M, Kutnowski M, Futeral B, Gianakopoulos X, Kraytman M, Gregoir W. Prevention of postoperative deep-vein thrombosis by low-dose heparin in open prostatectomy. *Urological Research* 1980, **8**(4):219-21. *(Guideline Ref ID: VANDENDRIS1980)*

537. Venous Thrombosis Clinical Study Group. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. *The Lancet* 1975, **2**(7924):45-51. *(Guideline Ref ID: ANON1975A)*

538. Verardi S, Cortese F, Baroni B, Boffo V, Casciani CU. (Role of low molecular weight heparin in the prevention of postoperative deep venous thrombosis. Our experience in 88 cases). *Giornale di Chirurgia* 1989, **10**(11):674-8. *(Guideline Ref ID: VERARDI1989)*

539. VERITY Steering Committee. Third Venous Thromboembolism Registry Summary Report (2006) http://www.verityonline.co.uk [accessed 2006]. *(Guideline Ref ID: VERITY2006)*

540. Ververeli PA, Sutton DC, Hearn SL, Rothman RR, Booth RE, Hozack WJ *et al*. Continuous passive motion after total knee arthroplasty: analysis of costs and benefits. *Clinical Orthopaedics and Related Research* 1995, **321**:208-15. *(Guideline Ref ID: VERVERELI1995)*

541. Vinazzer H, Loew D, Simma W, Brucke P. Prophylaxis of postoperative thromboembolism by low dose heparin and by acetylsalicylic acid given simultaneously. A double blind study. *Thrombosis Research* 1980, **17**(1-2):177-84. *(Guideline Ref ID: VINAZZER1980)*

542. Voigt J, Hamelmann H, Hedderich J, Seifert J, Buchhammer T, Kohler A. (Effectiveness and side effects of low-molecular weight heparin-dihydroergotamine in preventing thromboembolism in abdominal surgery). *Zentralblatt fur Chirurgie* 1986, **111**(21):1269-305. *(Guideline Ref ID: VOIGT1986)*

543. von Hospenthal J, Frey C, Rutishauser G, Gruber UF. (Prevention of thromboembolic complications in transurethral resection of the prostate). *Urologe Ausgabe A* 1977, **16**(2):88-92. *(Guideline Ref ID: VONHOSPENTHAL1977)*

544. von Tempelhoff GF, Harenberg J, Niemann F, Hommel G, Kirkpatrick CJ, Heilmann L. Effect of low molecular weight heparin (Certoparin) versus unfractionated heparin on cancer survival following breast and pelvic cancer surgery: A prospective randomized double-blind trial. *International Journal of Oncology* 2000, **16**(4):815-24. *(Guideline Ref ID: VONTEMPELHOFF2000)*

545. Wade WE. Cost effectiveness of danaparoid compared with enoxaparin as deep vein thrombosis prophylaxis after hip replacement surgery. *American Journal of Orthopedics* 1999, **28**(4):229-31. *(Guideline Ref ID: WADE1999)*

546. Wade WE, Chisholm MA. Cost effectiveness of deep venous thrombosis prophylaxis after hip fracture. *American Journal of Orthopedics* 2000, **29**(5):397-9. *(Guideline Ref ID: WADE2000C)*

547. Wade WE, Hawkins DW. Cost effectiveness of outpatient anticoagulant prophylaxis after total hip arthroplasty. *Orthopedics* 2000, **23**(4):335-8. *(Guideline Ref ID: WADE2000A)*

548. Wade WE, Spruill WJ, Leslie RB. Cost analysis: fondaparinux versus preoperative and postoperative enoxaparin as venous thromboembolic event prophylaxis in elective hip arthroplasty. *American Journal of Orthopedics* 2003, **32**(4). *(Guideline Ref ID: WADE2003)*

549. Wade WE, Spruill WJ, Leslie RB. Cost analysis of fondaparinux versus enoxaparin as venous thromboembolism prophylaxis in hip fracture surgery. *American Journal of Therapeutics* 2004, **11**(3):194-8. *(Guideline Ref ID: WADE2004)*

550. Ward B, Pradhan S. Comparison of low molecular weight heparin (Fragmin) with sodium heparin for prophylaxis against postoperative thrombosis in women undergoing major gynaecological surgery. *Australian & New Zealand journal of obstetrics & gynaecology* 1998, **38**(1):91-2. *(Guideline Ref ID: WARD1998A)*

551. Warlow C. Venous thromboembolism after stroke. *Am Heart J* 1978, **96**(3):283-5. *(Guideline Ref ID: WARLOW1978)*

552. Warwick D, Bannister GC, Glew D, Mitchelmore A, Thornton M, Peters TJ *et al*. Perioperative low-molecular-weight heparin. Is it effective and safe. *Journal of Bone and Joint Surgery British Volume* 1995, **77**(5):715-9. *(Guideline Ref ID: WARWICK1995A)*

553. Warwick D, Harrison J, Glew D, Mitchelmore A, Peters TJ, Donovan J. Comparison of the use of a foot pump with the use of low-molecular-weight heparin for the prevention of deep-vein thrombosis after total hip replacement. A prospective, randomized trial. *Journal of Bone and Joint Surgery American Volume* 1998, **80**(8):1158-66. *(Guideline Ref ID: WARWICK1998)*

554. Warwick D, Harrison J, Whitehouse S, Mitchelmore A, Thornton M. A randomised comparison of a foot pump and low-molecular-weight heparin in the prevention of deep-vein thrombosis after total knee replacement. *Journal of Bone and Joint Surgery British Volume* 2002, **84**(3):344-50. *(Guideline Ref ID: WARWICK2002)*

555. Warwick D, Williams MH, Bannister GC. Death and thromboembolic disease after total hip replacement. A series of 1162 cases with no routine chemical prophylaxis. *Journal of Bone and Joint Surgery British Volume* 1995, **77**(1):6-10. *(Guideline Ref ID: WARWICK1995)*

556. Watcha MF, White PF. Economics of anesthetic practice. *Anesthesiology* 1997, **86**(5):1170-96. *(Guideline Ref ID: WATCHA1997)*

557. Wautrecht JC, Macquaire V, Vandesteene A, Daoud N, Golzarian J, Capel P. Prevention of deep vein thrombosis in neurosurgical patients with brain tumors: a controlled, randomized study comparing graded compression stockings alone and intermittent sequential compression. Correlation with pre- and postoperative fibrinolysis: preliminary results. *International Angiology* 1996, **15**:5-10. *(Guideline Ref ID: WAUTRECHT1996)*

558. Weiss V, Jekiel M, Ritschard J, Bouvier CA. Prevention de la maladie thrombo-embolique post-operatoire par les anti-agregeants en chirurgie gynecologique. *Medecine et Hygiene* 1977, **35**:943-4. *(Guideline Ref ID: WEISS1977)*

559. Weitz J, Michelsen J, Gold K, Owen J, Carpenter D. Effects of intermittent pneumatic calf compression on postoperative thrombin and plasmin activity. *Thrombosis and Haemostasis* 1986, **56**(2):198-201. *(Guideline Ref ID: WEITZ1986)*

560. Welin-Berger T, Bygdeman S, Mebius C. Deep vein thrombosis following hip surgery. Relation to activated factor X inhibitor activity: effect of heparin and dextran. *Acta Orthopaedica Scandinavica* 1982, **53**(6):937-45. *(Guideline Ref ID: WELINBERGER1982)*

561. Welzel D, Wolf H, Koppenhagen K. Antithrombotic defense during the postoperative period. Clinical documentation of low molecular weight heparin. *Arzneimittel-Forschung* 1988, **38**(1):120-3. *(Guideline Ref ID: WELZEL1988)*

562. Westrich GH, Jhon PH, Sánchez PM. Compliance in using a pneumatic compression device after total knee arthroplasty. *American Journal of Orthopedics* 2003, **32**(3):135-40. *(Guideline Ref ID: WESTRICH2003)*

563. White RH, Zhou H, Gage BF. Effect of age on the incidence of venous thromboembolism after major surgery. *Journal of Thrombosis and Haemostasis : JTH* 2004, **2**(8):1327-33. *(Guideline Ref ID: WHITE2004)*

564. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thrombosis and Haemostasis* 2003, **90**(3):446-55. *(Guideline Ref ID: WHITE2003)*

565. Wiig JN, Solhaug JH, Bilberg T, Bjerkeset T, Edwin B, Gruner OP *et al*. Prophylaxis of venographically diagnosed deep vein thrombosis in gastrointestinal surgery. Multicentre trials 20 mg and 40 mg enoxaparin versus dextran. *European Journal of Surgery* 1995, **161**(9):663-8. *(Guideline Ref ID: WIIG1995)*

566. Wille JP, Jorgensen LN, Crawford M. Asymptomatic postoperative deep vein thrombosis and the development of

postthrombotic syndrome. A systematic review and meta-analysis. *Thrombosis and Haemostasis* 2005, **93**(2):236-41. *(Guideline Ref ID: WILLE2005)*

567. Wille-Jorgensen P, Hauch O, Dimo B, Christensen SW, Jensen R, Hansen B. Prophylaxis of deep venous thrombosis after acute abdominal operation. *Surgery, Gynecology & Obstetrics* 1991, **172**(1):44-8. *(Guideline Ref ID: WILLEJORGENSEN1991)*

568. Wille-Jørgensen P, Thorup J, Fischer A, Holst-Christensen J, Flamsholt R. Heparin with and without graded compression stockings in the prevention of thromboembolic complications of major abdominal surgery: a randomized trial. *British Journal of Surgery* 1985, **72**(7):579-81. *(Guideline Ref ID: WILLEJORGENSEN1985)*

569. Williams JT, Palfrey SM. Cost effectiveness and efficacy of below knee against above knee graduated compression stockings in the prevention of deep vein thrombosis. *Phlebologie* 1988, **41**(4):809-11. *(Guideline Ref ID: WILLIAMS1988)*

570. Williams JW, Eikman EA, Greenberg SH, Hewitt JC, Lopez CE, Jones GP *et al*. Failure of low dose heparin to prevent pulmonary embolism after hip surgery or above the knee amputation. *Annals of Surgery* 1978, **188**(4):468-74. *(Guideline Ref ID: WILLIAMS1978)*

571. Williams-Russo P, Sharrock NE, Haas SB, Insall J, Windsor RE, Laskin RS *et al*. Randomized trial of epidural versus general anesthesia: outcomes after primary total knee replacement. *Clinical Orthopaedics & Related Research* 1996,(331):199-208. *(Guideline Ref ID: WILLIAMSRUSSO1996)*

572. Wilson NV, Das SK, Kakkar VV, Maurice HD, Smibert JG, Thomas EM *et al*. Thrombo-embolic prophylaxis in total knee replacement. Evaluation of the A-V Impulse System. *Journal of Bone and Joint Surgery British Volume* 1992, **74**(1):50-2. *(Guideline Ref ID: WILSON1992)*

573. Wilson YG, Allen PE, Skidmore R, Baker AR. Influence of compression stockings on lower-limb venous haemodynamics during laparoscopic cholecystectomy. *British Journal of Surgery* 1994, **81**(6):841-4. *(Guideline Ref ID: WILSON1994A)*

574. Wirth T, Schneider B, Misselwitz F, Lomb M, Tüylü H, Egbring R *et al*. Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): Results of a randomized controlled trial. *Arthroscopy* 2001, **17**(4):393-9. *(Guideline Ref ID: WIRTH2001A)*

575. Wood EH, Prentice CR, McGrouther DA, Sinclair J, McNicol GP. Trial of aspirin and RA233 in prevention of post-operative deep vein thrombosis. *Thrombosis et Diathesis Haemorrhagica* 1973, **30**:18-24. *(Guideline Ref ID: WOOD1973)*

576. Wood KB, Kos PB, Abnet JK, Ista C. Prevention of deep-vein thrombosis after major spinal surgery: a comparison study of external devices. *Journal of Spinal Disorders* 1997, **10**(3):209-14. *(Guideline Ref ID: WOOD1997)*

577. Woolson ST, Watt JM. Intermittent pneumatic compression to prevent proximal deep venous thrombosis during and after total hip replacement. A prospective, randomized study of compression alone, compression and aspirin, and compression and low-dose warfarin. *Journal of Bone and Joint Surgery American Volume* 1991, **73**(4):507-12. *(Guideline Ref ID: WOOLSON1991)*

578. Wu TK, Tsapogas MJ, Jordan FR. Prophylaxis of deep venous thrombosis by hydroxychloroquine sulfate and heparin. *Surgery, Gynecology & Obstetrics* 1977, **145**(5):714-8. *(Guideline Ref ID: WU1977)*

579. Xabregas A, Gray L, Ham JM. Heparin prophylaxis of deep vein thrombosis in patients with a fractured neck of the femur. *Medical Journal of Australia* 1978, **1**(11):620-2. *(Guideline Ref ID: XABREGAS1978)*

580. Yoo MC, Kang CS, Kim YH, Kim SK. A prospective randomized study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement. *International Orthopaedics* 1997, **21**(6):399-402. *(Guideline Ref ID: YOO1997)*

581. Zanasi R, Fioretta G, Ciocia G, Bergonzi M. Prevention of deep venous thrombosis in orthopedic surgery: effects of defibrotide. *Clinical Therapeutics* 1988, **10**(4):350-7. *(Guideline Ref ID: ZANASI1988)*

582. Zekert F. Eigene klinische beobachtungen bei thromboembolieprophylaxe mit acetylsalicylsaure in der unfallchirurgie. In: Zekert F, ed. *Thrombosen, Embolien und Aggregationshemmer in der Chirurgie*, 1975. pp 88-96. Stuttgart: Schattauer. *(Guideline Reference ID: Ref ID: ZEKERT1975A)*

583. Zekert F. Prophylaxe von phlebothrombosen und lungenembolien mit aggregationshemmern. In: Zekert F, ed. *Thrombosen, Embolien und*

*Aggregationshemmer in der Chirurgie*, 1975. pp 75-88. Stuttgart: Schattauer. *(Guideline Reference ID: Ref ID: ZEKERT1975)*

584. Zekert F, Hofbauer F, Mühlbacher F. Thromboembolie-prophylaxe in der abdominalchirurgie. *MMW Münchener medizinische Wochenschrift* 1980, **122**(43):1495-8. *(Guideline Ref ID: ZEKERT1980)*

585. Zekert F, Schemper M, Neumann K. Acetylsalicylic acid in combination with dihydroergotamine for preventing thromboembolism. *Haemostasis* 1982, **11**(3):149-53. *(Guideline Ref ID: ZEKERT1982)*

586. Ziemski JM, Kostrzewska E, Marchlewski S, Wieczorek K, Rudowski W, Michalski R *et al.* (Efficacy of small doses of heparin given during 2 to 6 days in the prevention of postoperative deep vein thrombosis). *Polski Tygodnik Lekarski* 1979, **34**(5):161-4. *(Guideline Ref ID: ZIEMSKI1979)*

587. Zufferey P, Laporte S, Quenet S, Molliex S, Auboyer C, Decousus H *et al.* Optimal low-molecular-weight heparin regimen in major orthopaedic surgery. A meta-analysis of randomised trials. *Thrombosis and Haemostasis* 2003, **90**(4):654-61. *(Guideline Ref ID: ZUFFEREY2003)*

**APPENDICES**

Appendices can be found in a separate document.