Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing

Clinical Guideline

Methods, evidence and recommendations

June 2012

Commissioned by the National Institute for Health and Clinical Excellence

Royal College of Physicians
Setting higher medical standards
Royal College of Nursing
RCS
ADVANCING SURGICAL STANDARDS
RCGP Royal College of General Practitioners
NHS Evidence
accredited provider
NHS Evidence - provided by NICE
www.evidence.nhs.uk

Published by the National Clinical Guideline Centre at
The Royal College of Physicians, 11 St Andrews Place, Regents Park, London, NW1 4BT

First published June 2012

Contents

Guideline development group members **8**

Acknowledgments **9**

Abbreviations **10**

1 Introduction **12**

2 Development of the guideline **14**

2.1 What is a NICE clinical guideline? 14

2.2 Remit 14

2.3 Who developed this guideline? 15

2.4 What this guideline covers 15

2.5 What this guideline does not cover 15

2.6 Relationships between the guideline and other NICE guidance 16

3 Methods **17**

3.1 Developing the review questions and outcomes 17

3.2 Searching for evidence 20

3.2.1 Clinical literature search 20

3.2.2 Health economic literature search 20

3.3 Evidence of effectiveness 21

3.3.1 Inclusion/exclusion 21

3.3.2 Methods of combining clinical studies 22

3.3.3 Appraising the quality of evidence by outcomes 23

3.3.4 Grading the quality of clinical evidence 25

3.3.5 Study limitations 25

3.3.6 Inconsistency 26

3.3.7 Indirectness 26

3.3.8 Imprecision 27

3.4 Evidence of cost-effectiveness 28

3.4.1 Literature review 28

3.4.2 Undertaking new health economic analysis 30

3.4.3 Cost-effectiveness criteria 31

3.5 Developing recommendations 31

3.5.1 Research recommendations 32

3.5.2 Validation process 32

3.5.3 Updating the guideline 32

3.5.4 Disclaimer 32

3.5.5 Funding 32

4 Guideline summary **33**

4.1 Algorithms 33
4.2 Key priorities for implementation 35
4.3 Full list of recommendations 37
4.4 Key research recommendations 41
5 Diagnosis of deep vein thrombosis 42
5.1 Introduction 42
5.2 Clinical probability scores (clinical scores) 42
5.2.1 In people with suspected DVT, what is the effectiveness of clinical probability scores in ruling out DVT? 43
5.3 D-dimer 44
5.3.1 In people with suspected DVT, what is the effectiveness of D-dimer in ruling out DVT? 45
5.4 Ultrasound 47
5.4.1 In people with suspected DVT, what is the effectiveness of ultrasound in ruling out DVT? 48
5.5 Recommendations and link to evidence 54
5.6 Summary of research recommendations 67
6 Diagnosis of pulmonary embolism 68
6.1 Introduction 68
6.2 Clinical probability scores and D-dimers 68
6.2.1 In people with suspected PE, can we safely rule out further imaging based on clinical probability score and D-dimer assay? 70
6.3 Ventilation perfusion scans 72
6.3.1 In people with suspected PE, what is the effectiveness of ventilation perfusion scans in ruling out PE? 73
6.4 Computed tomography (CT) scans 77
6.4.1 In people with suspected PE, what it is the effectiveness of CT scans in ruling out PE? 78
6.5 Economic evidence 79
6.6 Recommendations and link to evidence 81
7 Pharmacological interventions 95
7.1 Introduction 95
7.1.1 What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed DVT? 95
7.1.2 What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed PE? 95
7.2 Pharmacological interventions for the initial phase of treatment 95
7.2.1 Initial phase of treatment: Matrix of treatment comparisons 96
7.2.2 Fondaparinux vs LMWH 96
7.2.3 Fondaparinux vs UFH 98

7.2.4 LMWH vs UFH 100
7.3 Pharmacological interventions for the continuation phase of treatment 109
7.3.1 Matrix of treatment comparisons 109
7.3.2 LMWH vs VKA 110
7.4 Duration of anticoagulation 117
7.4.1 Introduction 117
7.4.2 What is the optimal treatment duration for pharmacological interventions? 117
7.5 Recommendations and link to evidence 127
7.6 Summary of research recommendations 143
8 Thrombolytic therapy for DVT 144
8.1 Introduction 144
8.1.1 What is the effectiveness of thrombolytic therapy and mechanical thrombectomy to manage acute DVT? 144
8.2 Recommendations and link to evidence 149
8.3 Summary of research recommendations 151
9 Thrombolytic therapy for PE 152
9.1 Introduction 152
9.1.1 What is the effectiveness of open surgical thromboectomy, combination of mechanical and pharmacological thrombolysis, pharmacological thrombolytic therapy and heparin to manage acute PE? 153
9.2 Recommendations and link to evidence 158
9.3 Summary of research recommendations 161
10 Mechanical Interventions 162
10.1 Introduction 162
10.2 Vena caval filters 162
10.2.1 What is the clinical effectiveness of vena caval filters to manage venous thromboemobolic diseases in people that are unable to have pharmacological treatment? 162
10.3 Graduated compression stockings 167
10.3.1 What is the effectiveness of graduated compression stockings to prevent post thrombotic syndrome in people with venous thromboembolic diseases? 167
10.4 Recommendations and link to evidence 169
11 Patient information 177
11.1 Introduction 177
11.2 Patient information 177
11.2.1 Does the provision of information and support about the management of VTE improve patient outcomes? 177
11.3 Recommendations and link to evidence 180
12 Self-management and self-monitoring for patients treated with a vitamin K antagonist 185

12.1 Introduction 185
12.1.1 What is the effectiveness of self monitoring or self management compared to hospital/GP testing for long-term pharmacological treatments? 186
12.2 Recommendations and link to evidence 191
13 Investigations for cancer in VTE patients 193
13.1 Introduction 193
13.1.1 Do investigations for cancer in patients with spontaneous VTE (DVT or PE) improve patient outcomes (morbidity and mortality)? 194
13.2 Recommendations and link to evidence 197
Summary of research recommendations 202
14 Thrombophilia testing 203
14.1 Introduction 203
14.1.1 What is the effectiveness of thrombophilia testing in preventing recurrence of a venous thromboembolic event? 203
14.2 Recommendations and link to evidence 205
14.3 Thrombophilia testing for first degree relatives of people who had thromboembolic disease and thrombophilia 209
14.3.1 Does thrombophilia testing improve the outcomes of first degree relatives of people who have had thromboembolic disease and thrombophilia? 209
14.4 Recommendations and link to evidence 212
14.5 Research recommendations 213
15 References 214
16 Glossary 231

Guideline development group members

Name	Role
Gerard Stansby (Chair)	Professor of Vascular Surgery, Freeman Hospital and Newcastle University
Roshan Agarwal	Senior Lecturer/Honorary Consultant Medical Oncologist, Imperial College London
Susan Ballard	Patient/carer representative
David Berridge	Consultant Vascular Surgeon, Leeds General Infirmary
Christian Clark	Patient/carer representative. Member of the Atrial Fibrillation Task Force
Richard Day	Consultant Physician (Geriatrics), Poole Hospital NHS Foundation Trust
Hayley Flavell	Anticoagulant and Thrombosis Consultant Nurse, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust
Scott Harrison	Lead Pharmacist Anticoagulation, Oxford University Hospital NHS Trust
Beverley Hunt	Professor of Thrombosis and Haemostasis, King's College, London Medical Director of Lifeblood
David Keeling	Consultant Haematologist, Oxford University Hospitals NHS Trust
Nigel Langford	Acute Medical Physician, Sandwell and West Birmingham NHS Trust, City Hospital, Birmingham
Steven Moser	Consultant Radiologist, Imperial College Healthcare NHS Trust, London
Kat Noble	General Practitioner with a specialist interest in Emergency Care, NHS County Durham
Karen Sheares	Respiratory Consultant with an interest in pulmonary vascular diseases, Papworth Hospital NHS Foundation Trust

Expert adviser

Name	Role
Richard Graham	Consultant Radiologist, Royal United Hospital Bath

NCGC staff on the guideline development group

Name	Role
Joanna Ashe	Senior Information Scientist
Liz Avital	Associate Director
Caroline Blaine	Research Fellow (from January 2011)
Sara Buckner	Research Fellow (from January 2011)
Lee-Yee Chong	Senior Research Fellow
Elisabetta Fenu	Senior Health Economist
Caroline Hatchett	Research Fellow/Project Manager (from March 2011)
Jennifer Hill	Operations Director
Clare Jones	Senior Research Fellow/Project Manager (until March 2011)
Zahra Naqvi	Research Fellow (from January 2011)
Sarah Hodgkinson	Senior Research Fellow/Project Manager (until January 2011 and from February 2012)
Julie Neilson	Senior Research Fellow (until January 2011)

Acknowledgments

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

- Serena Carville (Senior Research Fellow/Project Manager, NCGC)
- Saoussen Ftouh (Senior Research Fellow/Project Manager, NCGC)
- Ralph Hughes (Health Economist, NCGC)
- Kate Kelley (Associate Director, NCGC)
- Susan Latchem (Operations Director, NCGC)
- Kate Lovibond (Senior Health Economist, NCGC)
- Grammati Sarri (Senior Research Fellow, NCGC)
- Carlos Sharpin (Head of Information Science/Research Fellow, NCGC)
- Ebenezer Tetteh (Senior Health Economist, NCGC)
- Maggie Westby (Clinical Effectiveness Lead, NCGC)
- David Wonderling (Head of Health Economics, NCGC)
- Hati Zorba (Project Coordinator, NCGC)

Abbreviations

Acronym	Abbreviation
AF	Atrial fibrillation
BMI	Body mass index
BNF	British National Formulary
CCA	Cost-consequences analysis
CCT	Controlled clinical trial
CEA	Cost-effectiveness analysis
CI(s)	Confidence interval(s)
COCP	Combined oral contraceptive pill
CT	Computerised tomography (scan)
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	CT pulmonary angiogram
CUA	Cost-utility analysis
DH	Department of Health
DVT	Deep vein thrombosis
ECG	Echocardiogram
ELISA	Enzyme linked immunosorbent assay
FP	Forest plot
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
HRQoL	Health related quality of life
HRT	Hormone replacement therapy
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IM/im	Intramuscular
INB	Incremental net benefit
INR	International normalised ratio
ITT	Intention to treat
IV/iv	Intravenous
LMWH	Low molecular weight heparin
LOS	Length of stay
LY	Life-year
MHRA	Medicines and Healthcare Products Regulatory Agency
MID	Minimal important difference
NCC-AC	National Collaborating Centre for Acute Care
NCGC	National Clinical Guideline Centre for Acute and Chronic Conditions (Formerly known as the

Acronym	Abbreviation
	National Collaborating Centre for Acute Care)
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMA	Network meta-analysis
NNT	Number needed to treat
NPV	Negative predictive value
OR	Odds ratio
PASA	NHS Purchasing and Supply Agency
PE	Pulmonary embolism
PICO	Framework incorporating patients, interventions, comparisons, outcomes
POCT	Point of care test
PPIP	Patient and Public Involvement Programme
PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
PT	Prothrombin time
PTS	Post-thrombotic syndrome
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SC/sc	Subcutaneous
SP	Synthetic pentasaccharide
SR	Systematic review
UFH	Unfractionated heparin
US	Ultrasound scan
VKA	Vitamin K antagonist
V/Q	Ventilation perfusion scan
V/Q (SPECT)	Ventilation perfusion scan (single photon emission computerised tomography)
vs	Versus
VTE	Venous thromboembolism

1 Introduction

Venous thromboembolism (VTE) is a condition in which a blood clot (a thrombus) forms in a vein and then dislodges to travel in the blood (an embolus). A venous thrombus most commonly occurs in the deep veins of the legs or pelvis; this is then called a deep vein thrombosis (DVT). Blood flow through the affected vein can be limited by the clot, and it can cause swelling and pain in the leg. If it dislodges and travels to the lungs, to the pulmonary arteries, it is called a pulmonary embolism (PE), which in some cases may be fatal. VTE as a term includes both DVT and PE. Major risk factors for VTE include a prior history of DVT, age over 60 years, surgery, obesity, prolonged travel, acute medical illness, cancer, immobility, thrombophilia (an abnormal tendency for the blood to clot) and pregnancy.

VTE is an important cause of death and the prevention of VTE has recently been made a priority for the NHS.[95] It has been estimated that every year 25,000 people in the UK die from preventable hospital-acquired VTE [51] and that it causes over 500,000 deaths in Europe.[38] Non-fatal VTE is also important as it can cause serious longer-term conditions such as post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). PTS is a chronic condition characterised by symptoms and signs which develop after DVT due to damage to the deep veins and their valves.[114] Its manifestations range from minor skin changes, pain or swelling, to established leg ulceration. It affects 20%-40% of patients after DVT of the lower limb, can be debilitating to patients, and have a significant impact on their quality of life.[197] CTEPH is less common and is caused by obstruction of the pulmonary arteries due to PE. This puts excessive pressure on the heart which can be harmful for some patients, causing heart failure.

The diagnosis of VTE is not always straightforward as other conditions may have similar symptoms, thus highlighting the need for guidance on the diagnostic pathways used for the assessment of possible DVT and PE. Failure to diagnose a case of VTE correctly may result in a patient not receiving the correct treatment and potentially suffering a fatal PE as a result. This guideline includes advice on the Wells score, D-dimer measurement, ultrasound and radiological imaging. We have looked at the diagnostic pathways for PE and DVT separately but this guideline did not consider PE risk stratification or the outpatient management of PE as these were beyond our scope. We have focussed on proximal DVT rather than isolated calf vein DVT as the latter is less likely to cause PTS than proximal DVT and also less likely to embolise to the lungs.

The current standard practice for the treatment of VTE is anticoagulation. These drugs “thin” the blood and prevent further clotting. There is a wide variation in practice, but patients are usually given a brief course of heparin treatment initially while they start on a 3–6 month course of warfarin. Patients who have had recurrent VTE or who are at high risk of recurrence may be given indefinite treatment with anticoagulants to prevent further VTE episodes. However, anticoagulation treatment is not without risk, for example, the risk of bleeding, and requires the patient to have regular monitoring blood tests. There is a need for guidance about which patients should have such prolonged treatment and how the monitoring should be performed. In addition, there is a wide variation in practice regarding when to test for thrombophilia after VTE and controversy as to how thrombophilia should be managed if it is found on testing.

There is also the potential to dissolve the clots using drugs termed thrombolytics which can be achieved both for DVT and PE. Dissolving the clots in the pulmonary arteries may reduce the risk of fatal PE and longer term problems with CTEPH. In the case of DVT, thrombolysis may reduce the risk of fatal PE and PTS. However, the use of thrombolytics may cause side-effects such as bleeding and guidance is needed as to which patients may benefit from their use.

This guideline considers the aforementioned in adults (18 years and older) with a suspected or confirmed DVT or PE in primary, secondary and tertiary health-care settings. Within this guideline the following will be considered as special risk groups; people with cancer, people who misuse

intravenous drugs, residents of nursing homes, people with physical disabilities who have restricted movement following a VTE and those with learning disabilities who require long-term medication to be taken at home. In particular, people with cancer are at higher risk of developing VTE and may need special advice on how it should be managed, as they may not respond as well when treated with warfarin. Children, people younger than 18 years and pregnant women will not be considered. Prophylaxis against VTE is not addressed as it is already the subject of a NICE clinical guideline (CG92).

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through 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 review questions.

NICE 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 Clinical Guideline Centre (NCGC).
- The NCGC establishes 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 NCGC 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 lists the recommendations.
- Information for the public ('understanding NICE guidance' or UNG) is written using suitable language for people without specialist medical knowledge.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

'To produce a clinical guideline on the management of venous thromboembolic diseases, including the use of thrombophilia testing'.

2.3 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 (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Gerard Stansby in accordance with guidance from NICE.

The group met every 4-8 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 were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

2.4 What this guideline covers

The guideline will cover diagnostic tests for initial assessment of suspected VTE and interventions to manage venous thromboembolic diseases. Interventions covered include: mechanical interventions, pharmacological interventions, thrombolytic therapy, screening for undiagnosed malignancy in people with spontaneous venous thromboembolism, self-monitoring by patients on pharmacological treatment, information and support for patients and carers, and thrombophilia testing for patients after a previous VTE and for first-degree relatives of people with inherited thrombophilia and venous thromboembolic diseases.

The groups that will be covered include adults (18 years and older) with a suspected or confirmed DVT or PE. Within this population, the following groups have been identified as requiring special consideration: people with cancer, people who misuse intravenous drugs, residents of nursing homes and people with physical disabilities who have restricted movement following a VTE and people with learning disabilities who require long-term medication taken at home.

In addition first-degree relatives of people with inherited thrombophilia and venous thromboembolic diseases will be considered.

Healthcare settings include primary, secondary and tertiary settings.

For further details please refer to the scope in Appendix A and review questions in section 3.1.

2.5 What this guideline does not cover

This guideline does not cover:

- Prophylaxis against VTE
- DVT in the arms
- Cerebral vein thrombosis

- Splanchnic thrombosis
- Retinal vein thrombosis.

Groups that will not be covered include:

- Children and young people (younger than 18 years)
- Pregnant women.

2.6 Relationships between the guideline and other NICE guidance

Published guidance

- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults. NICE technology appraisal guidance 245 (2012).
- Venous thromboembolism: reducing the risk. NICE clinical guideline 92 (2010).
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults. NICE technology appraisal guidance 170 (2009).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. NICE technology appraisal guidance 157 (2008).

Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website)

- Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. NICE technology appraisal guidance. Publication expected July 2012.
- Rivaroxaban for the prevention of venous thromboembolism in people hospitalised for acute medical conditions. NICE technology appraisal guidance. Publication date to be confirmed..
- Dabigatran etexilate for the treatment of acute venous thromboembolic events. NICE technology appraisal guidance. Publication date to be confirmed.

3 Methods

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009[167].

3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and with a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG).

As outlined in the NICE Guidelines Manual, review questions were developed based on the key clinical areas identified in the scope (Appendix A). These were drafted by the NCGC technical team and refined and validated by the GDG through discussions to ensure that the right review questions are identified.

Often, the GDG found that several review questions can be generated for a single area within the scope. However, only 15 to 20 questions can be reasonably managed within the usual time frame of full clinical guideline development (18 months). Since it was not possible to cover all potentially important aspects, the GDG had to consider the relative importance of these and prioritise areas for developing review questions. This decision should take into consideration factors such as whether the area is a key clinical issue for the NHS, patient safety, cost (to the NHS), equality and variations in practice.

Review questions and outcome measures examined in this guideline are detailed in Table 1 and protocols can be found in Appendix C. Areas where no review questions were made include risk stratification of patients with PE, factors or tests results (e.g. d-dimer tests) associated with risk of recurrence of VTE, where patients should be managed and whether isolated calf vein DVT should be treated.

Further information about development of review questions is available in Chapter 4 of the NICE Guidelines Manual 2009.[167]

Table 1: Review questions and outcomes

Chapter	Review questions	Outcomes
Diagnosis (DVT)	In people with suspected DVT, what is the effectiveness of clinical probability scores in ruling out DVT?	Sensitivity Specificity PPV NPV 3 month VTE rate Mortality
Diagnosis (DVT)	In people with suspected DVT, what is the effectiveness of D-dimer in ruling out DVT?	Sensitivity Specificity PPV NPV 3 month VTE rate Mortality
Diagnosis (DVT)	In people with suspected DVT, what is the effectiveness of ultrasound in ruling out DVT?	Sensitivity Specificity

Chapter	Review questions	Outcomes
		PPV NPV 3 month VTE rate Mortality
Diagnosis (PE)	In people with suspected PE, can we safely rule out further imaging based on clinical probability score and D-dimer assay?	Prevalence of PE Missed cases
Diagnosis (PE)	In people with suspected PE, what is the effectiveness of CT scan in ruling out PE?	Sensitivity Specificity PPV NPV 3 month VTE rate Non diagnostic rate Mortality
Diagnosis (PE)	In people with suspected PE, what is the effectiveness of ventilation perfusion scans in ruling out PE?	Sensitivity Specificity PPV NPV 3 month VTE rate Non diagnostic rate Mortality
Pharmacological Interventions	What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed PE?	VTE related mortality All cause mortality Recurrent VTE rates Major bleeding Quality of life (validated scores) Chronic thromboembolic pulmonary hypertension Fatal bleed Intracranial bleed/haemorrhage Post thrombotic syndrome
Pharmacological Interventions	What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed DVT?	VTE related mortality (3 month, final end point) All cause mortality Recurrent VTE rates Major bleeding Quality of life (validated scores) Post thrombotic syndrome Fatal bleed Intracranial bleed/haemorrhage
Pharmacological Interventions	What is the optimal treatment duration for pharmacological interventions?	All cause mortality Major bleeding VTE related mortality Recurrent VTE rates Quality of life (validated scores) Fatal bleed Intracranial bleed/haemorrhage Post thrombotic syndrome
Thrombolytic	What is the effectiveness of	All cause mortality

Chapter	Review questions	Outcomes
therapy (DVT)	thrombolytic therapy and mechanical thrombectomy to manage acute DVT?	VTE related mortality – 3 months Major bleeding (fatal and intracranial) Recurrent VTE rates (up to 90 days) Quality of life (validated scores) Post thrombotic syndrome up to 10 years later Chronic thromboembolic Pulmonary hypertension Length of hospital stay Heparin induced thrombocytopenia
Thrombolytic therapy (PE)	What is the effectiveness of open surgical thromboectomy, combination of mechanical and pharmacological thrombolysis, pharmacological thrombolytic therapy and heparin to manage acute PE?	All cause mortality VTE related mortality Major bleeding (fatal and intracranial) Recurrent VTE rates Quality of life (validated scores) Post thrombotic syndrome up to 10 years later Chronic thromboembolic pulmonary hypertension Length of hospital stay Heparin induced thrombocytopenia
Mechanical Interventions	What is the effectiveness of vena caval filters to manage venous thromboembolic diseases in people that are unable to have pharmacological treatment?	VTE related mortality All cause mortality Recurrent VTE rates Major bleeding Quality of life (validated scores) Chronic thromboembolic pulmonary hypertension Fatal bleed Post thrombotic syndrome
Mechanical Interventions	What is the effectiveness of graduated compression stockings to prevent post thrombotic syndrome in people with venous thromboembolic diseases?	Post thrombotic syndrome Skin adverse events Compliance Fitting Quality of life VTE related mortality
Patient education	Does provision of information and support about management of VTE improve patient outcomes?	Quality of life Recurrent VTE Compliance Within target INR range Patient satisfaction Post thrombotic syndrome Perception of patients, including knowledge in how to manage condition using treatments Major bleeding
Self Monitoring and management	What is the effectiveness of self monitoring compared to hospital/GP testing for long-term pharmacological treatments?	Recurrent VTE Bleeding (major and minor) Percentage of INR out of range Percentage of time in range
Cancer Screening	Does investigating for cancer in patients with spontaneous VTE	Cancer related mortality Sensitivity of intensive cancer screening and any

Chapter	Review questions	Outcomes
	(DVT or PE) improve patient outcomes (morbidity and mortality)?	indicator of delays in cancer diagnosis such as early stage cancer detection (T1 and T2) Delay in cancer diagnosis (months)
Thrombophilia screening	What is the effectiveness of thrombophilia testing in preventing recurrence of a venous thromboembolic event?	VTE related mortality Symptomatic / asymptomatic PE Symptomatic DVT Recurrent VTE rates Psychological impact Patient preference or patient views
Thrombophilia screening	Does thrombophilia testing improve the outcomes of 1st degree relatives of people who had thromboembolic disease and thrombophilia?	VTE related mortality Symptomatic DVT Symptomatic/Asymptomatic PE Recurrent VTE rates Psychological impact (e.g. anxiety) Patient preference or patient views Pick up rates

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The Guidelines Manual 2009[167]. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language. All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. The additional subject specific database PsychInfo was used for the patient education question. All searches were updated on 1st August 2011. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix D.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to the guideline population in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA)

databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, from 2010, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix D. All searches were updated on 1st August 2011. No papers published after this date were considered.

3.3 Evidence of effectiveness

The Research Fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C).
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual 2009[167].
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix E).
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta-analysed, where appropriate and reported in GRADE (Grading of Recommendations Assessment, Development and Evaluation) profiles (for clinical studies) – see below for details.
  - Observational studies: data presented as a range of values in GRADE profiles.
  - Qualitative studies: each study summarised in a table (available in Appendix E) where possible, and the quality of included studies assessed against the NICE quality checklists for qualitative studies [167]. Key common themes between studies which were relevant to the review question were summarised and presented with a comment of the quality of studies contributing to the themes in the main guideline document. GRADE does not have a system for rating the quality of evidence for qualitative studies or surveys, and therefore there are no GRADE quality ratings for the themes identified.

3.3.1 Inclusion/exclusion

The inclusion and exclusion criteria were considered according to the PICO used in the protocols, see Appendix C for full details.

A major consideration in determining the inclusion and exclusion criteria in the protocol was the applicability of the evidence to the guideline population. The populations included in the review may differ for each review question, depending on the applicability of the data. See "Indirectness", section 3.3.7.

Laboratory studies were excluded because the populations used (volunteers, animals or *in vitro*) are artificial and not comparable to the population we were making recommendations for. These studies would undoubtedly be of very low quality as assessed by GRADE and therefore low quality randomised controlled trials (RCTs), cohort studies or GDG consensus opinion was considered preferable.

Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded.

3.3.2 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes. The continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p < 0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where there was heterogeneity and a sufficient number of studies, sensitivity analyses were conducted based on risk of bias and pre-specified subgroup analyses were carried out as defined in the protocol. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals (CIs) were reported and meta-analysis was undertaken with the mean difference and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. Where p values were reported as “less than”, a conservative approach was undertaken. For example, if p value was reported as “$p < 0.001$”, the calculations for standard deviations were based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook 121 ‘Missing standard deviations’ were applied as the last resort.

For binary outcomes, absolute differences in event rates were also calculated using the GRADEpro software using total event rate in the control arm of the pooled results and presented in the “Clinical Summary of Findings Table”.

Pre-specified subgroup analyses were conducted for populations of interest. These are groups where it had been identified that the interventions were likely to have different effect (effect modifiers), rather than prognostic factors. Although prognostic factors are usually not good candidates for subgrouping in meta-analysis, it is often impossible to completely predict whether a potential difference in effect is due to a difference in how the intervention may work in a group, or in how it will affect all outcomes; for example active cancer is a prognostic factor, but can also possibly affect how anticoagulants work. When such subgroups are identified, studies were subgrouped to observe whether there might be differences in effects between different groups of patients.

If there were many clinical variations between studies in terms of population, intervention comparison and therefore any heterogeneity observed would be difficult to explain, the GDG decide a priori that the underlying assumption of fixed effects, which assumed that all the studies were measuring the same effect, is violated. Random effects analysis may be preferred because this model assumes there were random variations between studies and within study instead of assuming that all the studies were measuring the same effect (as in fixed effect model). This model is considered more conservative (with wider CIs). However, random effects analysis gave larger weights to smaller studies; and these studies (which often have higher risks of biases) have more weight than if conducted as a fixed effect analysis. Therefore, sensitivity tests were conducted with fixed effect model to ensure no important variations which could change decision making. In addition, sensitivity tests to exclude studies with high risks of biases were conducted when appropriate.

Data synthesis for diagnostic test accuracy review

For diagnostic test accuracy studies, the outcomes reported depends on the review question and purpose of the test. The outcomes reported may include: sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio, pre- and post-test probabilities, or numbers of patients missed (False negative). In cases where the outcomes were not reported, 2 by 2 tables were constructed from raw data to allow calculation of these accuracy measures, and these are presented in the evidence tables (see Appendix E).“Test and treat” designs were considered as appropriate for some review questions, and the relevant patient important outcomes from these strategies were reported where appropriate.

As the meta-analysis methods of diagnostic outcome was a developing field and was not a standard analysis of NICE guidelines at the time of the guideline development, the data was not pooled [167]. Results from diagnostic accuracy studies were entered into Review Manager 5.0, and the results are shown graphically.

3.3.3 Appraising the quality of evidence by outcomes

After appropriate pooling of the results for each outcome across all studies, the quality of the evidence for each outcome was evaluated and presented using an adaptation of the GRADE toolbox’[87]. The software (GRADEpro) developed by the international GRADE working group was used to record the assessment of the evidence quality for each outcome.

In this guideline, findings were summarised using two separate tables. The “Quality Assessment” table includes details of the quality assessment. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it is clear there was a risk of bias. Each outcome was examined separately for the quality elements listed and defined in Table 2and each graded using the quality levels listed in Table 3. The main criteria considered in the rating of these elements are discussed below (see Grading of Evidence in section 3.3.4). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment of quality of evidence for each outcome listed in section 3.3.4.[87]

The “Clinical Summary of Findings” table includes pooled outcome data (where appropriate), an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In the Clinical Summary of Findings table, the columns for intervention and control indicate the total of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N; numerator = total number of events, denominator = total number of patients across studies) are shown with percentages (note: this is not the results of meta-analysis).

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide CIs around the estimate of the effect relative to the clinically important threshold.

Quality element	Description
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

3.3.4 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.

The rating was then downgraded for the specified criteria: study limitations, inconsistency, indirectness, imprecision and publication bias. These criteria are detailed in Table 5. Observational studies were upgraded if there was a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have “serious” or “very serious” risk of bias was rated down -1 or -2 points respectively.

The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.

The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following section.

3.3.5 Study limitations

The main limitations for RCTs are listed in Table 5.

The decision of downgrading depends on whether methodological limitations had resulted in potentially important risks of bias for an outcome. For example, it is well accepted that investigator blinding and/or participant blinding was impossible to achieve in some interventions (e.g. patient education or monitoring. Nevertheless, open-label would still be downgraded if this is an important risk of bias (for example if the outcome was subjective, or if other factors can affect the performance of the interventions). This is important to maintain a consistent approach in quality rating across the guideline.

Table 5: Study limitations of RCTs

Limitation	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number, etc).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated.
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Carry-over effects in cross-over trials • Recruitment bias in cluster randomised trials.

3.3.6 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square $p<0.1$ or I- squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I- square and Chi square values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gives a plausible explanation of heterogeneity, the quality of evidence was not downgraded.

3.3.7 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

In deciding what evidence should be included in the review, the GDG took into account availability of information from populations, interventions, or comparisons which may not be as exactly stated in the review question. For example, studies conducted among all patients with taking oral anticoagulant should offer information to the effectiveness of patient information or self-monitoring or management programmes. These studies were included in the review, but the outcomes were downgraded to indicate indirectness: we are not certain whether the information obtained from this population is directly applicable to the VTE population. For further details and any exceptions are detailed in the review protocols, see Appendix C.

3.3.8 Imprecision

Results are often imprecise when studies include relatively few patients and few events and thus have wide CIs around the estimate of effect. This, in turn, may mean that we are uncertain if there is an important difference between interventions or not. If this is the case, the evidence may be considered to be of lower quality of the evidence lower than it otherwise would be because of resulting uncertainty in the results.

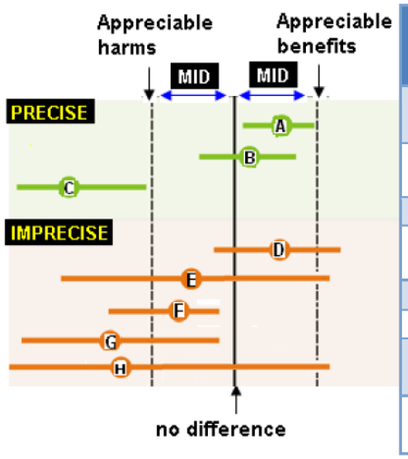
The thresholds of important benefits or harms, or the minimal important difference (MID) for an outcome are important considerations for determining whether there is a "clinically important" difference between interventions and in assessing imprecision. For continuous outcomes, the MID is defined as "the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in the management" [87,108,218,219]. An effect estimate larger than the MID is considered to be "clinically important". For dichotomous outcomes, the MID is considered in terms of changes in both absolute and relative risks.

The difference between two interventions, as observed in the studies, was compared against the MID when considering whether the findings were of "clinical importance"; this is useful to guide decisions. For example, if the effect size was small (less than the MID), this finding suggests that there may not be enough difference to strongly recommend one intervention over the other based on that outcome.

The CI for the pooled or best estimate of effect was considered in relation to the MID, as illustrated in Figure 1. Essentially, if the CI crossed the MID threshold, there was uncertainty in the effect estimate in supporting our recommendations (because the CI was consistent with two decisions) and the effect estimate was rated as imprecise.

For the purposes of this guideline, an intervention is considered to have a clinically important effect with certainty if the whole of the 95% CI describes an effect of greater magnitude than the MID.

Figure 1 illustrates how the clinical importance of effect estimates were considered along with imprecision, and the usual way of documenting this is in the evidence statements throughout this guideline. Results are imprecise when studies include relatively few patients and few events and thus have wide CIs around the estimate of the effect relative to the clinically important threshold.



Position of confidence interval	Evidence statement
A	...there are fewer/more ....but the **difference is not clinically important.**
B	....it is **unlikely** that there is a difference of clinical importance .....
C	..there is a **clinically important** fewer /more events ...
D	..it is **uncertain** whether there is a clinically important difference...
E	...It is **very uncertain** whether there is a difference ....
F	...there is a decrease of **uncertain** clinical importance in .....
G	..there is decrease of which is **may be of /likely to be** clinical importance ....
H	*... the decrease is potentially* clinically important, *but there is considerable/too much uncertainty...*

Figure 1: Illustration of precise and imprecision outcomes based on the CI of outcomes in a forest plot

MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms. The CIs of the top three points of the diagram were considered precise because the upper and lower limits did not cross the MID. Conversely, the bottom three points of the diagram were considered imprecise because all of them crossed the MID and reduced our certainty of the results. The effect estimates of the top three examples (A-C) were considered precise because neither the upper or lower confidence limits crossed the MID. Conversely, the bottom five examples (D to H) were considered imprecise because the CI crossed the MID(s) in each case, and this reduced our certainty of the results.

The default thresholds suggested by GRADE were a relative risk reduction of 25% (relative risk of 0.75 for negative outcomes) or a relative risk increase of 25% (risk ratio 1.25 for positive outcomes) for binary outcomes. For this guideline, the GDG adopted the default threshold suggested by GRADE, unless more information was available from the literature, or the absolute risks indicated that the default values are inappropriate. For example, when events rates are very low, the relative risk may have large CIs, but the CIs of the absolute number may be narrow. The GDG interpreted the risk ratio and 95% CI relative to the threshold, also taking into account the 95% CIs of the absolute effect estimates. For continuous outcomes, a standardised mean difference (SMD) of 0.5 was considered the MID for most outcomes.

3.4 Evidence of cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the economic literature
- Undertook new cost-effectiveness analyses in priority areas.

3.4.1 Literature review

The Health Economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual 2009[167].

- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix F.
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapters). See below for details.

3.4.1.1 Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix H from the Guidelines Manual, 2009)[167] and the health economics research protocol (Appendix C).

When no relevant economic analysis was found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implication of the recommendation made.

3.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from Appendix H, the Guidelines Manual[167]. It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. See Table 6 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity[177].

Table 6: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study*: • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making*: • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

*Limitations and applicability were assessed using the economic evaluation checklist from Appendix H, from the Guidelines Manual [167]

Where economic studies compare multiple strategies, results are not reported in the standard economic profile but are instead presented at the end of the relevant chapter in an alternative table. The study is summarised as a whole in a descriptive manner.

3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analyses were undertaken by the Health Economist in priority areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analyses were identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See Appendices H-I for details of the health economic analyses undertaken for the guideline.

3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money[168].

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance[168].

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

3.5 Developing recommendations

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

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix E and F.
- Summary of clinical and economic evidence and quality (as presented in Chapters 5 to 14).
- Forest plots (Appendix G).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix H and I).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits and harms, quality of evidence, and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on consensus. Expert advisors were invited to provide advice on how to interpret the identified evidence. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were made through discussions in the GDG, or methods of formal consensus were applied. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The main considerations specific to each recommendation are outlined in the Evidence to Recommendation Sections preceding the recommendation section in each chapter.

3.5.1 Research recommendations

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
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

3.5.2 Validation process

The guidance is subject to an eight week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

3.5.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will ask a National Collaborating Centre or the National Clinical Guideline Centre to advise NICE's Guidance executive whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.5.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

3.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

4 Guideline summary

4.1 Algorithms

Figure 2: Diagnosis of DVT algorithm

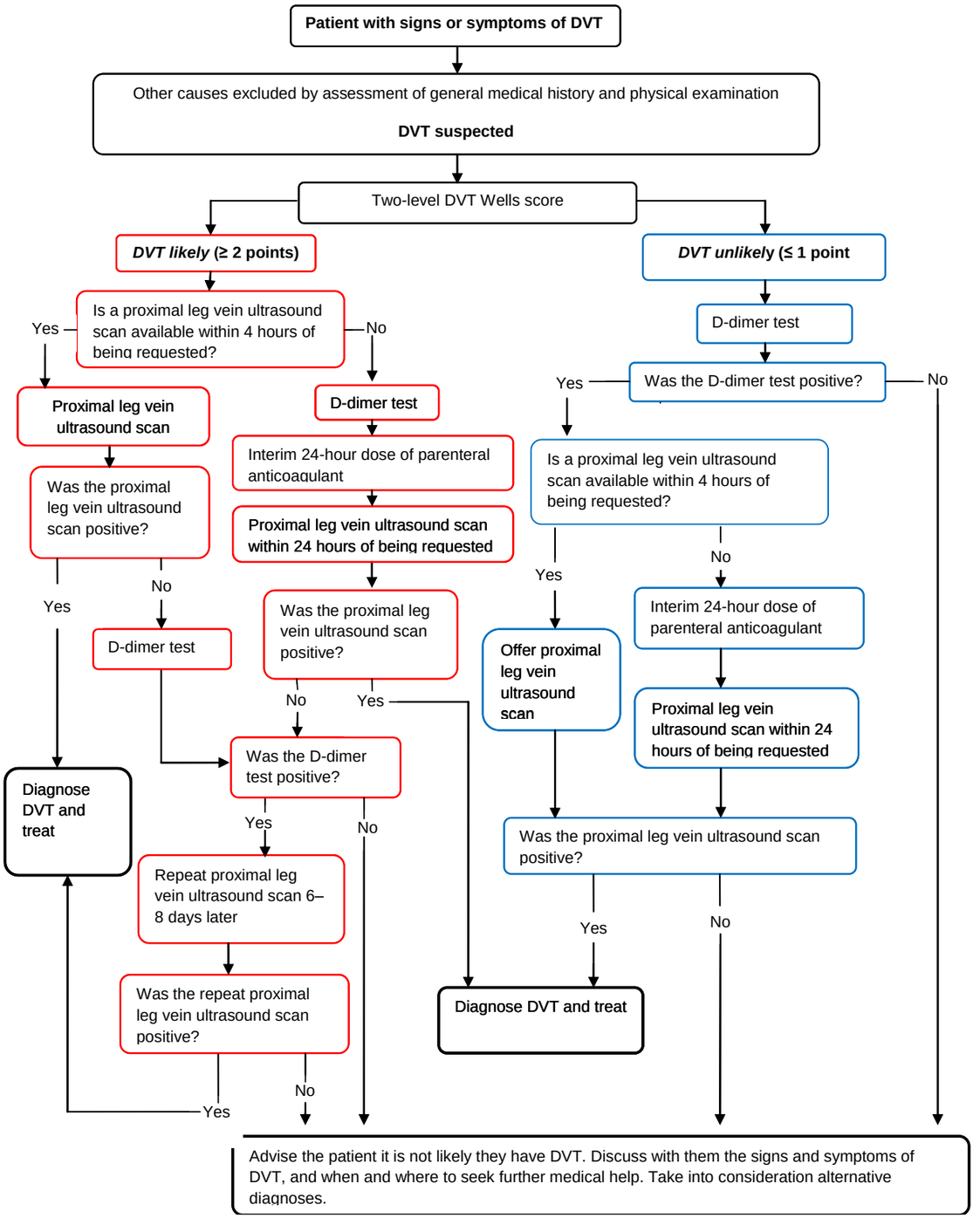
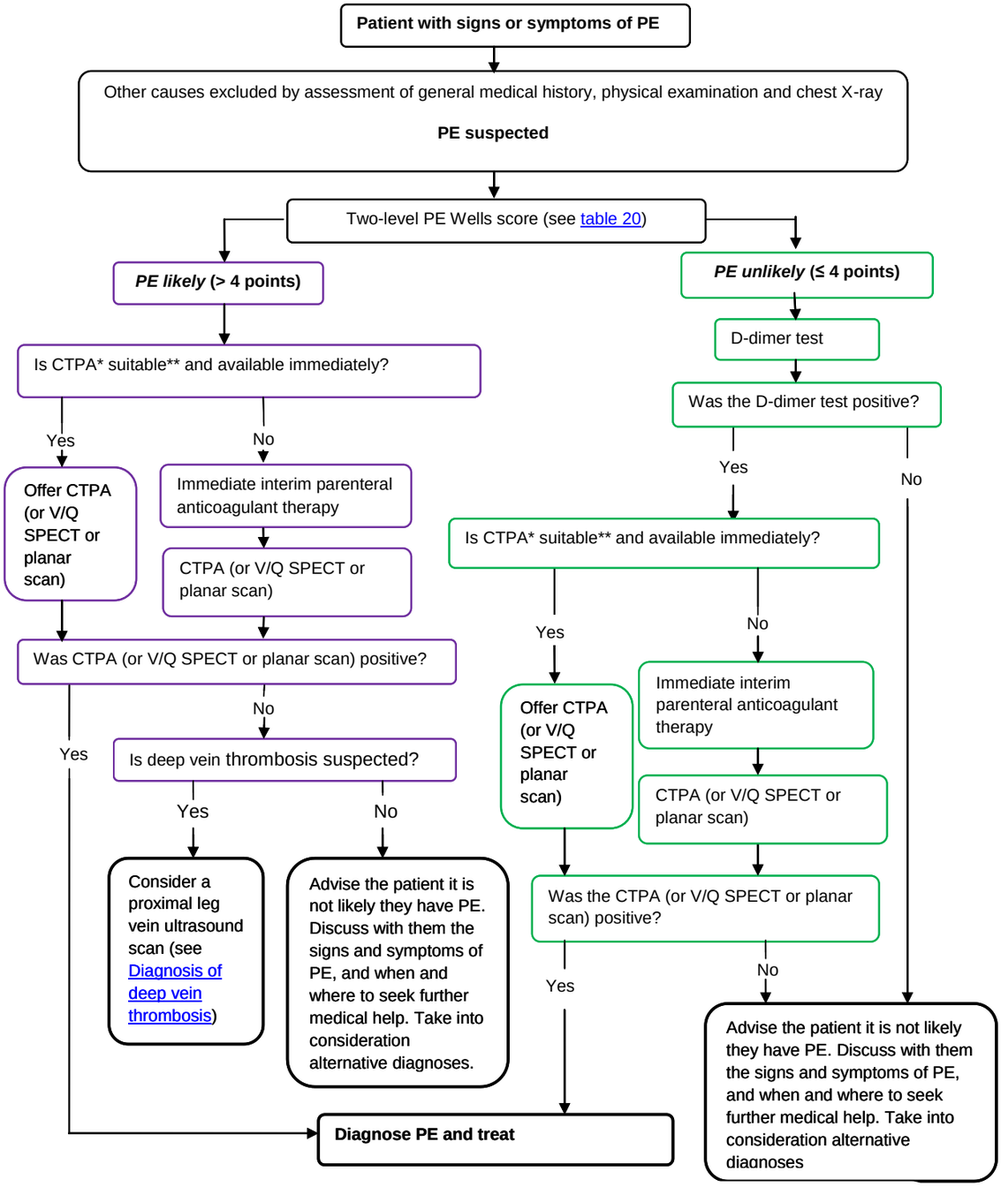


Figure 3: Diagnosis of PE algorithm



*Computed tomography pulmonary angiogram

**For patients who have an allergy to contrast media, or who have renal impairment, or whose risk from irradiation is high , assess the suitability of V/Q SPECT† or, if not available, V/Q planar scan, as an alternative to CTPA.

†Ventilation/perfusion single photon emission computed tomography

4.2 Key priorities for implementation

From the full set of recommendations, the GDG selected ten key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The 2009 Guidelines Manual.[167] The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

Diagnostic investigations for deep vein thrombosis

- If a patient presents with signs or symptoms of deep vein thrombosis (DVT), carry out an assessment of their general medical history and a physical examination to exclude other causes.

- Offer patients in whom DVT is suspected and with a *likely* two-level DVT Wells score (see Table 7) **either**:
  - a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test **or**
  - a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.

  Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan.

- Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score (see Table 7) a D-dimer test and if the result is positive offer **either**:
  - a proximal leg vein ultrasound scan carried out within 4 hours of being requested **or**
  - an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.

Diagnostic investigations for pulmonary embolism

- Offer patients in whom PE is suspected and with a *likely* two-level PE Wells score (see Table 20) **either**:
  - an immediate computed tomography pulmonary angiogram (CTPA) **or**
  - immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.

  Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected.

- Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score (see Table 20) a D-dimer test and if the result is positive offer **either**:
  - an immediate CTPA **or**
  - immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.

Pharmacological interventions for deep vein thrombosis or pulmonary embolism

- Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:
  - For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.
  - For patients with an increased risk of bleeding consider UFH.
  - For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 21 and 22).

  Start the LMWH, fondaparinux or UFH as soon as possible and continue it for 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 17) is 2 or above for at least 24 hours, whichever is longer.

- Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months.[(a)] At 6 months, assess the risks and benefits of continuing anticoagulation.[(b)]

  (a) At the time of publication (June 2012) some types of LMWH do not have a UK marketing authorisation for 6 months of treatment of DVT or PE in patients with cancer. Prescribers should consult the summary of product characteristics for the individual LMWH and make appropriate adjustments for severe renal impairment or established renal failure. Informed consent for off-label use should be obtained and documented.

  (b) Although this use is common in UK clinical practice, at the time of publication (June 2012), none of the anticoagulants has a UK marketing authorisation for the treatment of DVT or PE beyond 6 months in patients with cancer. Informed consent for off-label use should be obtained and documented.

- Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.

- Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.

Thrombolytic therapy for deep vein thrombosis

- Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have:
  - symptoms of less than 14 days' duration **and**
  - good functional status **and**
  - a life expectancy of 1 year or more **and**
  - a low risk of bleeding.

Mechanical interventions

- Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications[(b)], and:
  - advise patients to continue wearing the stockings for at least 2 years.
  - ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions.
  - advise patients that stockings need to be worn only on the affected leg or legs.

(b) Prescribers should refer to specific product information and contraindications before offering graduated compression stockings.

Investigations for cancer

- Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation (see recommendation 32).

4.3 Full list of recommendations

1. If a patient presents with signs or symptoms of deep vein thrombosis (DVT), carry out an assessment of their general medical history and a physical examination to exclude other causes.

2. If DVT is suspected, use the two-level DVT Wells score (see table 7) to estimate the clinical probability of DVT.

3. Offer patients in whom DVT is suspected and with a *likely* two-level DVT Wells score *either*:
   - a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test *or*
   - a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.

Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan.

4. Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score a D-dimer test and if the result is positive offer *either*:
   - a proximal leg vein ultrasound scan carried out within 4 hours of being requested *or*
   - an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.

5. Diagnose DVT and treat (see recommendations 16 to 27) patients with a positive proximal leg vein ultrasound scan.

6. Take into consideration alternative diagnoses in patients with:
   - an *unlikely* two-level DVT Wells score *and*
   - a negative D-dimer test *or*
   - a positive D-dimer test and a negative proximal leg vein ultrasound scan.
   - a *likely* two level DVT Wells score *and*
   - a negative proximal leg vein ultrasound scan and a negative D-dimer test *or*
   - a repeat negative proximal leg vein ultrasound scan.

Advise patients in these two groups that it is not likely they have DVT, and discuss with them the signs and symptoms of DVT and when and where to seek further medical help.

7. If a patient presents with signs or symptoms of PE, carry out an assessment of their general medical history, a physical examination and a chest X-ray to exclude other causes.

8. If PE is suspected, use the two-level PE Wells score (see Table 20) to estimate the clinical probability of PE.

9. Offer patients in whom PE is suspected and with a *likely* two-level PE Wells score *either*:
   - an immediate computed tomography pulmonary angiogram (CTPA) *or*
   - immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.

   Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected.

10. Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score a D-dimer test and if the result is positive offer *either*:
    - an immediate CTPA *or*
    - immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.

11. For patients who have an allergy to contrast media, or who have renal impairment, or whose risk from irradiation is high:
    - Assess the suitability of a ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scan or, if a V/Q SPECT scan is not available, a V/Q planar scan, as an alternative to CTPA.
    - If offering a V/Q SPECT or planar scan that will not be available immediately, offer immediate interim parenteral anticoagulant therapy.

12. Diagnose PE and treat (see recommendations 15 to 18 and 21 to 27) patients with a positive CTPA or in whom PE is identified with a V/Q SPECT or planar scan.

13. Take into consideration alternative diagnoses in the following two groups of patients:
    - Patients with an *unlikely* two-level PE Wells score and *either*
    - a negative D-dimer test *or*
    - a positive D-dimer test and a negative CTPA.
    - Patients with a *likely* two-level PE Wells score and *both*
    - a negative CTPA *and*
    - no suspected DVT.

    Advise these patients that it is not likely they have PE and discuss with them the signs and symptoms of PE, and when and where to seek further medical help.

14. If a patient presents with signs or symptoms of both DVT (for example a swollen and/or painful leg) and PE (for example chest pain, shortness of breath or haemoptysis), carry out initial diagnostic investigations for either DVT or PE, basing the choice of diagnostic investigations on clinical judgement.

15. Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:
    - For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose

adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.

- For patients with an increased risk of bleeding consider UFH.
- For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 21 and 22).

Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 17) is 2 or above for at least 24 hours, whichever is longer.

16. Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months[(a)]. At 6 months, assess the risks and benefits of continuing anticoagulation[(b)].

(a) At the time of publication (June 2012) some types of LMWH do not have UK marketing authorisation for 6 months of treatment of DVT or PE in patients with cancer. Prescribers should consult the summary of product characteristics for the individual LMWH and make appropriate adjustments for severe renal impairment or established renal failure. Informed consent for off-label use should be obtained and documented. (b) Although this use is common in UK clinical practice, at the time of publication (June 2012), none of the anticoagulants has a UK marketing authorisation for the treatment of DVT or PE beyond 6 months for patients with cancer. Informed consent for off-label use should be obtained and documented.

17. Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment (see recommendations 18 and 19).

18. Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.

19. Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.

20. Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have:
    - symptoms of less than 14 days' duration *and*
    - good functional status *and*
    - a life expectancy of 1 year or more *and*
    - a low risk of bleeding.

21. Consider pharmacological systemic thrombolytic therapy for patients with PE and haemodynamic instability (see also recommendation 15).

22. Do not offer pharmacological systemic thrombolytic therapy to patients with PE and haemodynamic stability (see also recommendation 15).

23. Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications[(b)], and:
    - advise patients to continue wearing the stockings for at least 2 years
    - ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions.
    - advise patients that stockings need to be worn only on the affected leg or legs.

(b) Prescribers should refer to specific product information and contraindications before offering graduated compression stockings.

24. Offer temporary inferior vena caval filters to patients with proximal DVT or PE who cannot have anticoagulation treatment, and remove the inferior vena caval filter when the patient becomes eligible for anticoagulation treatment.

25. Consider inferior vena caval filters for patients with recurrent proximal DVT or PE despite adequate anticoagulation treatment only after considering alternative treatments such as:
    - increasing target INR to 3-4 for long-term high-intensity oral anticoagulant therapy or
    - switching treatment to LMWH.

26. Ensure that a strategy for removing the inferior vena caval filter at the earliest possible opportunity is planned and documented when the filter is placed, and that the strategy is reviewed regularly.

27. Give patients having anticoagulation treatment verbal and written information about:
    - how to use anticoagulants
    - duration of anticoagulation treatment
    - possible side effects of anticoagulant treatment and what to do if these occur
    - the effects of other medications, foods and alcohol on oral anticoagulation treatment
    - monitoring their anticoagulant treatment
    - how anticoagulants may affect their dental treatment
    - taking anticoagulants if they are planning pregnancy or become pregnant
    - how anticoagulants may affect activities such as sports and travel
    - when and how to seek medical help.

28. Provide patients who are having anticoagulation treatment with an 'anticoagulant information booklet' and an 'anticoagulant alert card' and advise them to carry the 'anticoagulant alert card' at all times.

29. Be aware that heparins are of animal origin and this may be of concern to some patients*. For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement after discussing their suitability,advantages and disadvantages with the patient. [This recommendation is from Venous thromboembolism: reducing the risk (NICE clinical guideline 92)].

* See "Religion or belief: a practical guide for the NHS", website: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093133)

30. Advise patients about the correct application and use of below-knee graduated compression stockings, how long they should be worn and when they should be replaced.

31. Do not routinely offer self-management or self-monitoring of INR to patients who have had DVT or PE and are having treatment with a VKA.

32. Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:
    - a physical examination (guided by the patient's full history) *and*
    - a chest X-ray *and*
    - blood tests (full blood count, serum calcium and liver function tests) *and*
    - urinalysis.

33. Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation (see recommendation 32).

34. Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment.

35. Consider testing for antiphospholipid antibodies in patients who have had unprovoked DVT or PE if it is planned to stop anticoagulation treatment.

36. Consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment.

37. Do not offer thrombophilia testing to patients who have had provoked DVT or PE.

38. Do not routinely offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia.

4.4 Key research recommendations

1. What is the clinical and cost effectiveness of a whole-leg ultrasound scan compared with a proximal leg vein ultrasound scan in the diagnosis of acute DVT?

2. What is the clinical and cost effectiveness of long-term oral anticoagulation treatment in specific subgroups of patients with a first unprovoked VTE?

3. In patients with VTE and active cancer who have had 6 months of anticoagulation treatment with LMWH, what is the clinical benefit (in terms of VTE recurrence rates, all-cause mortality and major bleeding) and cost effectiveness of continued anticoagulation treatment with LMWH versus a VKA?

4. What is the clinical and cost effectiveness of clot removal using catheter-directed thrombolytic therapy or pharmacomechanical thrombolysis compared with standard anticoagulation therapy for the treatment of acute proximal DVT?

5. What is the clinical and cost effectiveness of systemic pharmacological thrombolysis compared with standard initial anticoagulation therapy in patients with confirmed PE and haemodynamic stability who present with right ventricular dysfunction?

5 Diagnosis of deep vein thrombosis

5.1 Introduction

The objective diagnosis of DVT depends on imaging using a combination of compression and colour flow (Doppler) ultrasound or, rarely nowadays, venography. However, because of the cost of these modalities and the increasing number of negative tests, strategies have been developed which can exclude the diagnosis in some patients without the need for diagnostic imaging. These rely on the use of information from clinical history and examination (a pre-test probability assessment) and assays to detect D-dimers. Pre-test probability assessment is usually with performed using a Wells' score.

5.2 Clinical probability scores (clinical scores)

Patients with a DVT may present with signs and symptoms such as swelling, pain, redness and warmth in the leg. The initial step for patients presenting with a possible DVT is to assess them for their individual pre-test probability, i.e. the likelihood that they have a DVT. This involves using a clinical probability score (also known as pre-test probability test/score, clinical scores or clinical prediction rule). A good clinical probability score helps to stratify people into different risk categories, so that the most appropriate diagnostics pathway or treatment pathways can be followed.

This review considered all validated clinical probability scores for patients with suspected DVT. However there are only a few clinical probability scores available for DVT. Many of these scores have a number of variations and are referred to in publications with different names. For example, the Wells Score is one of the most widely used and there are a few modifications in the exact choice of wording used in the score, items included, scoring systems and cut off points [236, 260,261]. The following are brief descriptions of two of the most commonly used versions of the DVT Wells score, where the "original" version use a three level risk stratification system while the newer version (which is referred to as "updated", "modified", "revised" or "two-levels" in publications) use two levels of risk stratification:

- Wells score (Original). In 1997, Wells et al[260] developed a nine component clinical prediction rule for DVT. Two points are deducted if an alternative diagnosis to DVT is at least as likely. This gives a possible score range of -2 to 8. There were three risk categories: "high" (a score of 3 or more) "intermediate" (1-2 points) and "low" (less than 1 point). This is also sometimes referred to as the Hamilton score, with a slight change of wording.

- Wells score (two-levels). In 2003 a further component, "previously documented DVT", was added to the original Wells score and instead of considering surgery within 4 weeks as a risk factor, the duration at risk was extended to within 12 weeks[261] (Table 7). This gives a possible score range of -2 to 9. Instead of three risk categories in the original version, this version only has two risk categories: "likely" (2 points or more) or unlikely (less than 2 points).

Table 7: Two-level DVT Wells Score (from Wells et al[261] with permission from author)

Clinical Feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2
Clinical probability simplified score	
DVT 'likely'	2 points or more
DVT 'unlikely'	1 point or less

5.2.1 In people with suspected DVT, what is the effectiveness of clinical probability scores in ruling out DVT?

See Evidence Tables in Appendix E.1.

5.2.1.1 Clinical evidence

Table 8: Clinical scores – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Wells score						
Sensitivity & Specificity [52,72,85,85,106,179,270]	26	Diagnostic	No serious limitation (a),(b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Negative predictive value (NPV) & positive predictive value (PPV) [52,72,106,179,270]	5	Diagnostic	No serious limitation (a),(b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
All scores						
3 months VTE rate	0	Diagnostic or RCT				
Mortality	0	Diagnostic or RCT				

(a) Goodacre 2006[85] pooled results from 25 cohorts in 24 studies, 21 used the original (three-level) Wells score, 2 used the two level Wells score

(b) Di Nisio 2006 [52] contained two cohorts; patients with and without cancer, while another study used both a slight modification of the original Wells score and the modified two level Wells score[238].

(c) A range of values obtained from different studies increasing uncertainty of the actual effect estimate.

Table 9: Wells score – Clinical summary of findings

Outcome	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Quality
Wells score	Pooled: 0.89(95% CI: 0.86 to 0.92) Range: 77-98	Pooled: 0.48(0.40 to 0.56) Range: 37-58	81.1-98.3	14.2-63.0	MODERATE
Wells score in cancer patient	96	26	90	48	MODERATE

(a) Values are ranges, unless specified as pooled. Data from the HTA reported were pooled in a meta-analysis.

5.2.1.2 Economic evidence

See section 5.4.1.2.

Using a Wells scoring system was a component of the most cost-effective algorithms identified in the economic evidence. In this analysis, the cost of performing a Wells score was assumed to be equivalent to 5 minutes of hospital consultant time (£6.83) in addition to the time taken to assess the patient's general history and conduct further examination.

5.2.1.3 Evidence statements

Clinical

Twenty six studies involving 13086 patients showed that the sensitivity and specificity for DVT Wells score ranged from 77% to 98% and 37 to 58% respectively. For the purpose of ruling out DVT, this means that 2 to 23 out of 100 patients with the disease will be missed with a DVT Wells score and this implies that this test can be considered for ruling out DVT in conjunction with another test. The specificity suggests that 42 to 63 out of 100 of people without DVT will be identified as having the condition, and this implies that this test is not suitable for the purpose of confirming the presence of DVT without further diagnostic testing. Only five of these studies reported negative and positive predictive values (MODERATE QUALITY).

In a cohort of cancer patients the sensitivity (96%) was higher but the specificity was 26%. This implies that that in this cohort of patients, only 4% of patients with cancer will be missed, but the test should not be used for confirming the presence of DVT in patients with cancer (MODERATE QUALITY).

Economic

Using a DVT Wells scoring system is part of a cost-effective diagnostic strategy. The cost of performing a Wells score is relatively low (£6.83).

5.3 D-dimer

Thrombus formation is normally followed by an immediate fibrinolytic response. The resultant generation of plasmin causes the release of fibrin degradation products (predominantly containing D-dimer) into the circulation. A negative D-dimer assay therefore implies that thrombosis is not occurring and thus has a role in excluding a diagnosis of DVT along with clinical scores and imaging. It should be noted that whilst a positive result can indicate thrombosis there may be other causes of a raised D-dimer including liver disease, inflammation, malignancy, pregnancy, trauma and recent surgery.

5.3.1 In people with suspected DVT, what is the effectiveness of D-dimer in ruling out DVT?

5.3.1.1 Clinical evidence

Pooled results from one meta-analysis which included studies up to year 2004 were included[85]. In addition, 14 prospective cohort studies from the year 2004 were found, of which 8 contributed new accuracy data.

Clinical Evidence tables can be found in Appendix E.2.

Table 10: D-dimer – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Meta-analysis: Pooled sensitivity and specificity[85]						
All D-dimer tests[85]	97	Meta-analysis of diagnostic cohorts	No serious limitations (a)	Serious inconsistency (b)	Serious indirectness (c)	No serious imprecision
ELISAs[85] (h)	*58*	*Sub-group data from meta-analysis*	*No serious limitations (a)*	*Serious inconsistency (b)*	*Serious indirectness (c)*	*No serious imprecision*
Latex assays[85]	*52*	*Sub-group data from meta-analysis*	*No serious limitations (a)*	*Serious inconsistency (b)*	*Serious indirectness (c)*	*No serious imprecision*
Whole-blood agglutination[85]	*29*	*Sub-group data from meta-analysis*	*No serious limitations (a)*	*Serious inconsistency (b)*	*Serious indirectness (c)*	*No serious imprecision*
Non pooled studies						
Sensitivity & Specificity [5,50,52,54,106,172,235,237]	8	Diagnostic	Serious limitations (d)	Serious inconsistency (e)	Serious indirectness (f)	Serious imprecision (g)
PPV or NPV[5,50,52,54,106,172,235,237]	8	Diagnostic	Serious limitations (d)	Serious inconsistency (e)	Serious indirectness (f)	Serious imprecision (g)
3 month VTE rate	0	Diagnostic or RCT				
Mortality	0	Diagnostic or RCT				

(a) Reference standards used differ between cohorts, and were dependent on D-dimer or unclear in 14 cohorts (for details see evidence tables in appendix E.2). The threshold value for D-dimer was defined before analysis in 82 cohorts, was defined after analysis in ten and was not clear in seven. D-dimer was measured blind to the reference standard in 43 cohorts and measurement was unclear in 56. The reference standard was interpreted blind to the D-dimer result in 50 cohorts and interpretation was unclear in 49. These potential limitations were considered not severe enough to further reduce our confidence in the estimate of effect.

(b) Meta-regression was conducted to investigate heterogeneity. Higher quality studies (prospective studies, those recruiting consecutive patients, those using venography as a reference standard, D-dimer and reference standard measured blind) tended to have higher specificity. Studies that determined the D-dimer threshold after data analysis had higher sensitivity. However, stratification by each significant predictor identified in the meta-regression did not explain the heterogeneity.

(c) The main meta-analysis included studies which are almost 20 years old, and all the various types of test (which may have different range of accuracies) are pooled together. The performance of different subgroups of tests was considered. It is likely that a newer test will have better diagnostic accuracy than an older test. The sensitivity and specificity of tests are also dependent on the characteristics of the population these tests are applied on. The studies included had a median prevalence of 36% (range 2 to 78 %)

(d) Various limitations in studies, such as unclear whether the same type of ultrasound scan was done for all patients, unclear whether investigators were blinded to the reference/index test and poor reporting of some studies.

(e) The range of sensitivity and specificity obtained from various studies were substantial.

(f) Unclear whether study patients are representative to the population recommended.

(g) Wide range of values obtained

(h) ELISA is an acronym for a type of D-dimer test called an "enzyme-linked immunosorbent assay"

Table 11: D-dimer – Clinical summary of findings

Outcome [(a)]	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Quality
All D-dimer tests	Pooled: 90 (95% CI: 90 to 91) Range: 75 to 100	Pooled: 54.7 (95% CI: 54 to55) Range 26 to 83	16 to 64	90 to 100	LOW
ELISAs	Pooled: 94 (95% CI:93 to 95)	Pooled: 45 (95% CI:88 44 to 46)	-	-	LOW
Latex assays	Pooled: 89 (95% CI:88 to 90)	Pooled: 55 (95% CI:88 54 to 56)	-	-	LOW
Whole blood agglutination	Pooled: 87 (95% CI:88 85 to 88)	Pooled: 68 (95% CI:88 67 to 69)	-	-	LOW

(a) Values are ranges, unless specified as pooled. Data from the HTA reported were pooled in a meta-analysis[85].

5.3.1.2 Economic evidence

See section 5.4.1.2.

Using a D-dimer test was one of the components of the most cost-effective algorithms identified in the economic evidence. In this analysis, the cost of performing a D-dimer test was calculated as the cost of whole-blood agglutination D-dimer (£12.16) or laboratory-based D-dimer (£13.11), plus 5 minutes of consultant time (£6.83).

5.3.1.3 Evidence statements

Clinical

Eight studies involving over a thousand patients showed that the sensitivity and specificity for D-dimer tests ranged from 75% to 100% and 26% to 83% respectively. For the purpose of ruling out DVT, this means that 0 to 25 out of 100 patients with the disease will be missed with a D-dimer test and this implies that this test can be considered for ruling out DVT in conjunction with another test, but not on its own. The specificity suggests that 17 to 74 out of 100 people without DVT will be identified as having the condition and this implies that this test is not suitable for the purpose of confirming the presence of DVT (VERY LOW QUALITY).

In a meta-analysis, evidence from 97 studies involving thousands of patients showed that the 95% CI for sensitivity and specificity for all D-dimer tests ranged from 90% to 91% and 54% to 55% respectively. For the purpose of ruling out DVT, this means that 9 to 10 out of 100 patients with the disease will be missed with all D-dimer tests. This implies that these tests can be considered for ruling out DVT in conjunction with another test. The specificity suggests that 45 to 46 out of 100 people without DVT will be identified as having the condition and this implies that this test is not suitable for the purpose of confirming the presence of DVT (LOW QUALITY).

A subgroup of this meta-analysis, which had included 58 studies involving thousands of patients showed that the 95% CI for sensitivity and specificity for ELISAs ranged from 93% to 95% and 44% to 46% respectively. For the purpose of ruling out DVT, this means that 5 to 7 out of 100 patients with the disease will be missed with a D-dimer test and this implies that this test can be considered for ruling out DVT in conjunction with another test. The specificity suggests that 54 to 56 out of 100 people without DVT will be identified as having the condition and this implies that this test is not suitable for the purpose of confirming the presence of DVT (LOW QUALITY).

A subgroup of this meta-analysis, which had included 52 studies involving thousands of patients, showed that the 95% CI for sensitivity and specificity for latex assays ranged from 88% to 90% and 54% to 56% respectively. For the purpose of ruling out DVT, this means that 10 to 12 out of 100 patients with the disease will be missed with a D-dimer test and this implies that this test can be considered for ruling out DVT in conjunction with another test. The specificity suggests that 44 to 46 out of 100 people without DVT will be identified as having the condition and this implies that this test is not suitable for the purpose of confirming the presence of DVT (LOW QUALITY).

A subgroup of this meta-analysis, which had 29 studies involving thousands patients showed that the 95% CI for sensitivity and specificity for whole blood agglutination ranged from 85% to 88% and 67% to 69% respectively. For the purpose of ruling out DVT, this means that 12 to 15 out of 100 patients with the disease will be missed with a D-dimer test and this implies that this test can be considered for ruling out DVT in conjunction with another test. The specificity suggests that 31 to 33 out of 100 people without DVT will be identified as having the condition and this implies that this test is not suitable for the purpose of confirming the presence of DVT(LOW QUALITY).

Economic — D-dimer is a component of a cost-effective diagnostic strategy. The cost of performing a D-dimer test is relatively low (between £19 and £20).

5.4 Ultrasound

Ultrasonography has the advantage over venography of being non-invasive and has been shown to have a high sensitivity and specificity for proximal DVT. However, ultrasound does not identify calf vein DVT reliably. DVT involving calf veins which do not extend to the proximal veins rarely lead to clinically significant emboli but in those that do extend, the risk of PE is significant. This has led to two different ultrasound strategies for DVT diagnosis. Many clinicians deliberately restrict ultrasound to only look at the proximal veins and then perform a repeat test one week later in selected patients. The first test will detect any proximal thrombosis, a calf vein thrombus will remain undetected but a repeat scan one week later will pick up the clinically important ones that have extended. A second strategy is to scan the whole leg (proximal and calf veins). This means that no repeat ultrasound is required though it does subject more patients to anticoagulation. Both strategies are acceptable and safe.

Compression ultrasound consists of using gentle probe pressure to try and compress the vascular lumen. If no residual lumen is observed the vein is considered to be fully compressible, which indicates the absence of DVT. Duplex ultrasonography is similar but in addition a Doppler signal is used to determine blood flow characteristics. When the phasic (with respiration) pattern of venous blood flow is absent venous outflow obstruction is diagnosed. The images can be augmented by colour flow duplex imaging.

5.4.1 In people with suspected DVT, what is the effectiveness of ultrasound in ruling out DVT?

5.4.1.1 Clinical evidence

In this section we looked at two aspects of using ultrasound scans for the diagnosis of deep vein thrombosis:

1) Effectiveness of ultra sound scans compared to a reference standard such as venography in diagnosing DVT.

2) The effectiveness of whole leg ultrasound scan vs proximal leg vein ultrasound scan

The main source of clinical evidence is a large HTA meta-analysis of 100 cohorts of patients [85]. The review was updated with the inclusion of 6 additional studies [171,181,202,109,223,243,14.]

For the effectiveness of whole leg vs proximal leg vein ultrasound, only two RCTs were found [23,77.] Therefore, information from one of the cohort studies which presented the sensitivities and specificities of ultrasound scan in distal vein vs proximal vein were also reviewed.

See clinical evidence tables in Appendix E.3 for details of studies.

Table 12: Ultrasound – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Various ultrasound techniques – meta-analysis [85]						
Sensitivity & Specificity	98	Meta-analysis of diagnostic cohorts	No serious limitations	No serious inconsistency	Serious indirectness (a)	No serious imprecision
NPV & PPV	98	Meta-analysis of diagnostic cohorts	No serious limitations	No serious inconsistency	Serious indirectness (a)	No serious imprecision
Various ultrasound techniques (studies conducted after HTA review)						
Sensitivity & Specificity (c) 171,181,202,109,223,243,14	6	Diagnostic	Serious limitations (b)	No serious inconsistency	Serious indirectness (d)	Serious imprecision (e)
NPV & PPV(c) 171,181,202,109,223,243,14	6	Diagnostic	Serious limitations (b)	No serious inconsistency	Serious indirectness (d)	Serious imprecision (e)

(a) Goodacre (2006)[85] was a HTA review which included 100 cohorts. 22 cohorts had compression ultrasonography alone, 5 cohorts had colour Doppler alone, 16 had continuous-wave Doppler alone, 28 had duplex (compression and colour Doppler), 25 had triplex (compression, colour Doppler and continuous-wave Doppler) and 4 had other techniques. Due to a large variation in the type of patients included (meta-analysis also included asymptomatic patients, for example) and techniques used, the results may not be directly to each setting whether there recommendation is applied.

(b) Various limitations in studies such as unclear whether investigators were blinded to the reference/index test and small sample size. In addition, some studies may have included convenience samples rather than consecutive patients. One study[14] had reported by limbs rather than patients. Only 44 patients were included in the study.

(c) Ricci (2004)[202], Shiver (2010)[223] undertook ultrasound of the proximal area, Aywak (2007)[14], Naz (2005) [172] and Ricci (2004)[202] undertook ultrasound of the whole-leg area and Tomkowski (2007)[243] gave results for the proximal and distal areas of the leg.

(d) Studies recruited patients who were suspected of PE [223] or had confirmed PE [181] rather than patients who were presenting with suspected DVT. In addition, one study recruited consecutive patients from a prophylaxis study [243] – a screening study rather than a study in patient with suspected DVT. Meta-regression analysis of the HTA meta-analysis suggested that sensitivity decreases in cohorts which are asymptomatic.

Table 13: Ultrasound versus venography – Clinical summary of findings

Outcome	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Quality
Various ultrasound techniques (pooled results from meta-analysis)	89.7 (89 to 91)	93.8 (93-94)	-	-	MODERATE
Various ultrasound techniques (studies conducted after HTA review)	60-89	71-100	75-100	84-100	VERY LOW

Table 14: Ultrasound scan for detecting proximal and calf vein DVT– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Various ultrasound techniques – meta-analysis [85]						
Proximal veins - Sensitivity & Specificity [85]	98	Meta-analysis of diagnostic cohorts	No serious limitations	No serious inconsistency	Serious indirectness (a)	No serious imprecision
Proximal veins – NPV & PPV [85]	98	Meta-analysis of diagnostic cohorts	No serious limitations	No serious inconsistency	Serious indirectness (a)	No serious imprecision
Distal veins - Sensitivity & Specificity [85]	98	Meta-analysis of diagnostic cohorts	No serious limitations	No serious inconsistency	Serious indirectness (a)	No serious imprecision
Distal veins – NPV & PPV [85]	98	Meta-analysis of diagnostic cohorts	No serious limitations	No serious inconsistency	Serious indirectness (a)	No serious imprecision
Various ultrasound techniques (studies conducted after HTA review)						
Proximal veins - Sensitivity & Specificity [243(b)]	1	Diagnostic	Serious limitations (c)	No serious inconsistency	No serious indirectness	No serious imprecision
Proximal veins – NPV & PPV [243(b)]	1	Diagnostic	Serious limitations (c)	No serious inconsistency	No serious indirectness	No serious imprecision
Distal veins - Sensitivity & Specificity [243(b)]	1	Diagnostic	Serious limitations (c)	No serious inconsistency	No serious indirectness	No serious imprecision
Distal veins – NPV & PPV [243(b)]	1	Diagnostic	Serious limitations (c)	No serious inconsistency	No serious indirectness	No serious imprecision

(a) Due to a large variation in the type of patients included (meta-analysis also included asymptomatic patients, for example) and techniques used, the results may not be directly to each setting whether there recommendation is applied.

(b) Proximal and distal were reported separately in the paper.

(c) Acutely ill medical patients, uncertainty in applicability of results.

Table 15: Ultrasound scan for detecting proximal and calf vein DVT – Clinical summary of findings

Outcome	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Quality
Various ultrasound techniques – meta-analysis [85]					
Proximal vein DVT	94.2(93- 95)	-	-	-	MODERATE
Distal vein DVT	63.5(60-67)	-	-	-	MODERATE
Various ultrasound techniques (studies conducted after HTA review)					
Proximal vein DVT	60	90	0.64	75	MODERATE
Distal vein DVT	29	99	1.37	50	MODERATE

Table 16: Proximal versus whole leg ultrasound scan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Incidence of DVT detected [77]	1	RCT	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]
3 month VTE rate[77]	1	RCT	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Very serious imprecision [(b)]

(a) No details of randomisation method or allocation concealment. Open label study.
(b) The CI crossed MID points and/or event rates are very low.

Table 17: Proximal versus whole leg ultrasound scan – Clinical summary of findings

Outcome	Proximal ultrasound	Whole leg ultrasound	Relative risk	Absolute risk	Quality
Incidence of DVT detected	59/257 (23%)	99/264 (37.5%)	RR 0.61 (0.47-0.8)	146 fewer per 1000 (from 75 fewer to 199 fewer)	LOW
3 month VTE rate	4/198 (2%)	2/165 (1.2%)	RR 1.67(0.31-8.99)	8 more per 1000 (from 8 fewer to 97 more)	VERY LOW

Table 18: Proximal leg vein ultrasound scan plus D-dimer versus whole leg ultrasound scan – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Initial prevalence of DVT[23]	1	RCT	Serious limitation[(a)]	No serious inconsistency	No serious indirectness	Serious imprecision[(b)]
3 month VTE rate [23]	1	RCT	Serious limitation[(a)]	No serious inconsistency	No serious indirectness	Very serious imprecision[(c)]

(a) Unclear whether clinicians blinded to patient history. Patients with abnormal ultrasound excluded from study.
(b) CI crossed MID and/or event rates are very low.

Table 19: Proximal ultrasound plus D-dimer versus whole leg ultrasound – Clinical summary of findings

Outcome	Proximal ultrasound plus D-dimer	Whole leg ultrasound scan	Relative Risk	Absolute risk	Quality
Initial prevalence of DVT	231/1045 (22.1%)	278/1053 (26.4%)	RR 0.84 (0.72 – 0.97)	42 fewer per 1000 (from 8 fewer to 74 fewer)	LOW
3 month VTE rate	7/814 (0.9%)	9/775 (1.2%)	RR 0.74 (0.28 – 1.98)	3 fewer per 1000 (from 8 fewer to 11 more)	VERY LOW

5.4.1.2 Economic evidence

Several economic studies were found which compared different strategies to diagnose DVT. As a good cost-utility study from the UK was available[85] we excluded those studies not presenting effectiveness estimates in terms of QALYs[22,42,73,93,96,97,120,124] or with limited applicability to the UK NHS setting.[188,242]

The decision model developed by Goodacre et al (2006)[85] compared several algorithms based on different combinations of available tests and scores: Wells score, D-dimer, ultrasound scan (full-leg or above-knee), venography, plethysmography, and on decision rules. More details on the study are reported in the economic evidence tables in Appendix F.

We excluded strategies with plethysmography as this test was not included in our review questions.

Important inputs of the model and their sources were:

- accuracy of tests based on the meta-analysis of the same study, assuming independence from previous ones (with the exception of the accuracy of D-dimer which depends on the previous Wells score categorisation);
- baseline probabilities of events such as proximal and distal DVT, and PE based on follow-up studies;
- effectiveness and adverse events of treatment for DVT from meta-analyses;
- costs of tests and treatments from national data;
- decrements in quality of life due to PTS and intracranial haemorrhage obtained from a small study; non-fatal non-intracranial haemorrhage and non-fatal PE were based on expert opinion.

The results of the model are reported in the economic evidence table (Appendix F); all the algorithms came out better than the no testing strategy. Generally, algorithms that discharge patients with a low Wells score and a negative D-dimer resulted in a high net benefit. At the NICE threshold of £20,000/QALY the optimal algorithm (algorithm 21) consisted of a Wells stratification into high versus low or intermediate probability; people with high risk of DVT would undergo venography and treated or discharged according to the result of this test; people with low or intermediate risk of DVT would undergo a SimpliRED D-dimer test followed by venography if positive or discharge if negative.

Venography is not widely used currently and is invasive; if strategies based on this test are excluded two algorithms become optimal.

In the first one (algorithm 9), a latex D-dimer is performed; if negative the categorisation of the Wells score will determine whether the patient will be discharged (low/intermediate score) or undergo an ultrasound (high score). All the patients with a positive D-dimer will also undergo an ultrasound. In case of a positive ultrasound patients will be treated for DVT; if negative the test will be repeated.

The second optimal strategy (algorithm 16) starts with a Wells stratification followed by above-knee ultrasound for the high risk group; if the ultrasound is positive they will be treated while if negative they will undergo a SimpliRED D-dimer; people in the low/intermediate stratification will go directly to the D-dimer test. Patients will be discharged if this test is negative while they undergo another ultrasound if positive.

Both strategies described could be cost-effective as shown by the probabilistic sensitivity analysis and by the one-way sensitivity analysis on the prevalence of proximal DVT.

Conclusions from the study

The authors made some conclusions from the results of the study:

- The optimal strategy depends on the availability of venography. If the test is available, Algorithm 21 is the most cost-effective (Wells score – venography – D-dimer). If venography is not routinely available, Algorithm 9 (D-dimer – ultrasound scan/Wells score) or 16 (Wells – ultrasound scan/D-dimer) are the most cost-effective.
- If the prevalence of DVT is very low (<1%) testing for DVT is not cost-effective.
- D-dimer is cost-effective also when its specificity is lower (e.g. in patients with malignancy).
- If algorithm 16 is used, then a latex D-dimer assay maybe more cost-effective than ELISA or SimpliRED assays.
- Above-knee ultrasound with a repeat if negative is more cost-effective than a single above-knee or full-leg ultrasound.
- Repeat ultrasound is more cost-effective if performed on the basis of the D-dimer test.

The GDG had some concerns about the practicality of adopting algorithm 16. If this strategy was recommended, patients in the high risk group would have to wait to receive an ultrasound. If the wait is long, especially if the patient presents at hospital at the weekend or during a bank holiday, they would receive initial treatment while awaiting this test. This additional cost has not been captured in the model developed by Goodacre et al. (2006)[85] and the GDG thought it would make algorithm 16 less cost-effective under these circumstances. The GDG decided that if an ultrasound scan is not available within four hours, it would be more cost-effective to perform a D-dimer test on all patients, as this test can be performed quickly and at a low cost, whilst helping to reduce the number of patients requiring ultrasound scans and the number of unnecessary treatments.

5.4.1.3 Evidence statements

Clinical

Ultrasound vs reference standards

A very large meta-analysis of 100 cohorts of patients showed that the sensitivity and specificity for various ultrasound techniques were 89.7% and 93.8% respectively. For the purpose of ruling out DVT, this means that about 10 out of 100 patients with the disease will be missed with ultrasound and this implies that this test can be considered for ruling out DVT in conjunction with another test. The specificity suggests that 6 out of 100 people without DVT will be identified as having the condition and this implies that this test is suitable for the purpose of confirming the presence of DVT. The meta-analysis also suggested that sensitivity decreases in asymptomatic cohorts (screening studies) (MODERATE QUALITY).

Six studies involving about 300 patients showed that the sensitivity and specificity for various proximal ultrasound techniques ranged from 60% to 89% and 71% to 100% respectively. For the purpose of ruling out DVT, this means that 11 to 40 out of 100 patients with the disease will be missed with an ultrasound and this implies that this

test can be considered for ruling out DVT in conjunction with another test. The specificity suggests that 0 to 29 out of 100 people without DVT will be identified as having the condition and this suggests that ultrasound techniques were not consistently shown to be suitable for the purpose of confirming the presence of DVT (VERY LOW QUALITY).

Ultrasound scan for proximal and to distal leg veins DVT compared to reference standards

A very large meta-analysis of 100 cohorts of patients showed that the sensitivity of ultrasound techniques was 94.2% for detecting proximal vein DVTs and 63.5% in for distal vein DVTs compared to reference standards. For the purpose of ruling out DVT, this means that 6 out of 100 patients with proximal DVT will be missed with a proximal ultrasound test and this implies that this test can be considered for ruling out DVT in conjunction with another test. However, 37 out of 100 patients with distal DVT with be missed with a distal leg vein DVT. This implies that distal vein ultrasound is not adequate the purpose of detecting calf vein DVT (MODERATE QUALITY).

One study involving 160 patients who participated in a VTE prophylaxis study showed that the sensitivity and specificity for proximal ultrasonography was 60% and 90% respectively compared to venography (MODERATE QUALITY).

In contrast, the sensitivity and specificity for distal ultrasound tests was 29% and 99% respectively. For the purpose of ruling out DVT, this means that 71 out of 100 patients with the disease will be missed with a distal ultrasound test and this implies that this test is not effective in ruling out distal DVT (MODERATE QUALITY)

These studies suggest that ultrasound techniques are effective for ruling out proximal DVTs but not calf vein or distal DVTs.

Proximal vs whole leg ultrasound

Data from 283 patients in one study showed that there was a decrease which maybe of clinical importance in the incidence of DVT detected between proximal and whole leg ultrasound (LOW QUALITY).

In one study of 363 patients it is very uncertain whether there is a clinically important difference between proximal and whole leg ultrasound in 3 month VTE rate (VERY LOW QUALITY).

Proximal plus D-dimer vs whole leg ultrasound scan

Data from 1589 patients in one study showed that there was a decrease of uncertain clinical importance in the initial prevalence of DVT in the group who had proximal ultrasound plus D-dimer compared to the group who received a whole leg ultrasound (LOW QUALITY).

Data from 2098 patients in one study showed that it is uncertain if there was a clinically important difference between proximal and whole leg ultrasound in 3 month VTE rate (VERY LOW QUALITY).

Economic

After risk stratification with a Wells score, offering an ultrasound scan is cost-effective in the high risk group or after a positive D-dimer test. It is cost-effective to treat patients who had a positive ultrasound. Above-knee ultrasound with a repeat if negative is more cost-effective than a single above-knee or full-leg ultrasound. This evidence has potentially serious limitations and partial applicability.

5.5 Recommendations and link to evidence

Recommendations	1. If a patient presents with signs or symptoms of deep vein thrombosis (DVT), carry out an assessment of their general medical history and a physical examination to exclude other causes.
Relative values of different outcomes	The most important issue is to investigate for alternative diagnosis which explains the symptoms.
Trade off between clinical benefits and harms	Assessing general medical history and physical examination does not present any harm to the patient and may pick up or exclude other possible causes for suspected DVT. Completing this step of the diagnosis is crucial, as it will direct the consecutive diagnostic pathway to be undertaken for the patient. Ruling out alternative diagnosis for DVT was allocated twice the points of other items assessed in the Wells Score- performing this step correctly is crucial in the correct use of Wells Score and pre-test probability scoring.
Economic considerations	The assessment of the general medical history and the physical examination are associated with some increase in the clinician's time but they are not expected to increase costs considerably. In addition, these assessments are helpful in ruling out PE and consequently avoiding further more costly tests and radiation exposure.
Quality of evidence	This is a supporting recommendation based on GDG consensus.
Other considerations	This recommendation was chosen as a key priority for implementation (KPI) because the clinical experience suggests that not all patients receive a medical and physical examination to exclude other possible causes. This should be standard practice and needs to be implemented for all patients presenting with DVT signs and symptoms. The GDG discussed that this happens for patients who present with a PE, which is why the analogous recommendation in the PE diagnosis chapter was not identified as a KPI. The GDG have prioritised this recommendation as a key priority for implementation as they considered that it has a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes equalities and means patients reach critical points in the care pathway more quickly.

Recommendations	2. If DVT is suspected, use the two-level DVT Wells score (see table 7) to estimate the clinical probability of DVT.
Relative values of different outcomes	The GDG considered sensitivity to be the most important outcome, so that a DVT can be safely ruled out.
Trade off between clinical benefits and harms	There is a trade off between giving additional unnecessary tests and missed cases. The GDG considered the cost of missed cases of DVT outweighed the burden of additional testing. The GDG considered both the original (three-level) and the modified (two-level) Wells scores for DVT and examined each point in both versions. The two-level Wells score was more relevant and up to date because it included new criteria that take into account previous history of DVT and also expanded the duration post surgery considered as a risk from 4 weeks to 12 weeks. These changes are consistent with our latest understanding of VTE risks. The GDG understands that a larger proportion of patients may be categorised as requiring an ultrasound scan using the two level Wells score for DVT due to the addition of a new item, an expansion of the length of duration of risk post surgery, and a lowering of cut off points for further ultrasound scanning from 3 to 2 points. On the other hand, lowering the pre-test probability in the "unlikely" group means that patients can be more safely ruled out when combined with the use of D-dimer tests.
Economic considerations	Based on a decision model comparing different sequences of tests, stratifying patients according to their Wells score is cost-effective as this helps to target more expensive tests (e.g. ultrasound scan) to the high risk group. The cost of performing a Wells score is relatively low (£6.83). The evidence reviewed did not compare two-level with three level DVT Wells score and the economic model was based only on the three level score. The GDG decision to recommend the two level DVT Wells score was not based on cost-effectiveness but on other considerations (see 'Other considerations' section below).
Quality of evidence	Most of the studies published in this area were reviewed and pooled by the HTA. The main limitations of the evidence are the wide range of sensitivity values observed - this could have been contributed by the underlying heterogeneity of the study settings and study populations. The type of scores and scoring systems used in studies are also often not reported clearly. Most studies in Wells score used the three-level, original Wells score. The economic evidence has potentially serious limitations and partial applicability.
Other considerations	The use of clinical scores is considered a starting point and would be used in conjunction with other tests. When used in combination with D-dimer test, an "unlikely" Wells score, which puts a patient at a low pre-test probability, could safely rule out DVT. There is also less demand on the level of sensitivity required from the D-dimer test.[179,270] Practical considerations were taken into account by the GDG when making this recommendation: • The DVT Wells scores (original, three-level score and also the modified two-level) are the most widely validated pre-test probability scores and have been widely used in the NHS. • When a dichotomous scoring system is used (likely/unlikely), these are much easier to be implemented correctly because there is less chance of confusion

Recommendations	**2. If DVT is suspected, use the two-level DVT Wells score (see table 7) to estimate the clinical probability of DVT.**
	about what to do with the "moderate" group in the old system • The healthcare professional completing the score need to be trained, as the item "alternative diagnosis as likely as DVT" is awarded with a "-2" point – the item with highest weight in the scoring system. Therefore, the modified, two-level Wells score for DVT is recommended for use in this guideline. A copy of the score is available in the appendices (See Appendix K).

Recommendations	**3. Offer patients in whom DVT is suspected and with a *likely* two-level DVT Wells score *either*:** • **a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test *or*** • **a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.** **Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan.**
Relative values of different outcomes	The GDG considered the avoidance of undiagnosed and untreated DVT to be the most important outcome, followed by concerns about the number of additional diagnostic tests (which are non invasive, with few side effects) that patients receive. This recommendation is intended to follow up patients with the appropriate tests after the pre-probability testing with a DVT Wells score. The ability to correctly confirm and initiate treatment for patients with DVT while sending patients who do dot have DVT home without further imaging or treatments are considered the most important issues. Both sensitivity and specificity are important outcomes. In this situation, D-dimer was considered in the context of ruling out DVT.
Trade off between clinical benefits and harms	As sensitivity increases (less patients with DVT missed), the proportion of patients with a false positive test may increase (more patients sent for unnecessary further investigations and treatments and this is an important strain on the NHS resources). **D-dimer** D-dimer tests have relatively high sensitivity but low specificity (false positive results common). When the sensitivity of a d-dimer test increase, its specificity decreases. To be useful in the diagnosis of DVT, a D-dimer test has high sensitivity and high negative value - fewer people with DVT will be missed. Therefore, a negative D-dimer may be useful in excluding DVT but a positive D-dimer is of no diagnostic value, it merely mandates further testing. Whilst a negative D-dimer test is good enough to exclude the diagnosis of DVT in a patient with an "unlikely" pre-test clinical probability it is not good enough in those with a "likely" pre-test probability.

Recommendations	**3. Offer patients in whom DVT is suspected and with a *likely* two-level DVT Wells score *either*:** • **a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test *or*** • **a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.** **Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan.**
	Proximal leg vein ultrasound scan Proximal leg vein ultrasound scans are used as confirmatory tests in this pathway. Therefore both sensitivity and specificity are important, in order to ensure all DVTs are detected, and patients without DVT are not given heparin. The GDG had recommended proximal leg vein ultrasound scans as the clinical importance of picking up extra calf vein blood clots by scanning the whole leg is uncertain. Moreover, the evidence review suggested that ultrasound scan of calf veins are not very sensitive in picking up calf vein DVT. A repeat proximal leg vein scan is recommended to ensure that any clots propagating to the proximal veins are not missed. It is important to follow the sequence recommended to minimise the unnecessary use of ultrasound scans so that patients who need these scans can access them as soon as possible. Patient can be at risk of deterioration or at risk of a PE If a quick confirmation scan is not available. That is why anticoagulants are recommended if there is a delay in getting access to a scan.
Economic considerations	Based on a decision model comparing different sequences of tests, after risk stratification with a DVT Wells score, offering an ultrasound scan is cost-effective in the high risk group or after a positive D-dimer test. According to this model, offering a D-dimer test to patients who had a negative ultrasound scan is cost-effective. The cost of performing a D-dimer test is relatively low (between £19 and £20). Above-knee ultrasound with a repeat if negative is more cost-effective than a single above-knee or full-leg ultrasound scan. The four-hour limit to the ultrasound scan was not based on economic evidence but on safety considerations. The model was conducted using a three-level DVT Wells score but based on other considerations on implementation the GDG decided to recommend a two-level DVT Wells score.
Quality of evidence	**D-dimer** The majority of the evidence base comes from a large meta-analysis which pooled 97 diagnostic studies. The pooled sensitivity is 90%, indicating that 90% of patients with DVT will be correctly picked up. However, the main limitation of this evidence is this is a form of “average” sensitivity of all D-dimer tests. The actual sensitivity of tests varies between about 80% to more than 90%, depending on the specific type of technology used in the tests.

Recommendations	**3. Offer patients in whom DVT is suspected and with a *likely* two-level DVT Wells score *either*:** • **a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test *or*** • **a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.** **Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan.**
	Proximal leg vein ultrasound scan The quality of evidence ranged from very low to moderate for the various ultrasound strategies reviewed. These studies showed that ultrasound scans have high specificities, which makes them effective in confirming the presence of DVT. However, the sensitivity of the tests can vary a little between studies and average around 90%. The economic evidence has potentially serious limitations and partial applicability.
Other considerations	Proximal ultrasound will be used to confirm whether patients have DVT if they presented with DVT symptoms and accessed as "likely" risk of DVT using a two-level DVT Wells score. The GDG considered at length the implications of implementation and whether this affects current practice. The following factors were discussed and considered by GDG members: • It is important to diagnose and confirm DVT quickly. Treatment with LMWH exposes patients to side effects and is expensive (cost of drug and district nurse time). It is important not to put patients needlessly on LMWH. • It is necessary to find a safe and cost-effective strategy to identify which patients can be sent home safely (through DVT Wells score and D-dimer), and reduce the number of people referred for an ultrasound scan. • Access to ultrasound scan can be a problem, especially at weekends and outside normal working hours. Delays in accessing ultrasound scans are a potential problem and these delays need to be addressed and avoided. In situations where delay in access is unavoidable, strategies are required to ensure that patients are treated in the interim. • Therefore, while it is recognised that access to ultrasound scans can be a limitation, it was also agreed that this should not be a reason on its own to prevent recommending what is required in the best interest of patients, especially when this is a very cost effective strategy. The GDG had considered that since patients assessed as having a high risk of DVT will not be sent home even if a D-dimer is negative, it is best to prioritise sending this group of patients to ultrasound scans so that a diagnosis can be confirmed and treatment initiated promptly. • In patients with a "likely" DVT Wells score, patients with a positive ultrasound scan have DVT confirmed and need to be treated immediately, while patients with a negative ultrasound scan are offered a D-dimer to double check that there is a low risk of DVT before being sent home.

Recommendations	**3. Offer patients in whom DVT is suspected and with a *likely* two-level DVT Wells score *either*:** • **a proximal leg vein ultrasound scan carried out within 4 hours of being requested and, if the result is negative, a D-dimer test *or*** • **a D-dimer test and an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.** **Repeat the proximal leg vein ultrasound scan 6–8 days later for all patients with a positive D-dimer test and a negative proximal leg vein ultrasound scan.**
	The GDG also discussed that ultrasound techniques have important limitations in visualising iliac vein thrombosis. The current clinical understanding is this technique may not be effective if the relatively unusual situation of isolated iliac vein thrombosis is suspected. If this is suspected (for example, from changes in blood flow in the femoral vein), the usual practice is to investigate with other imaging methods such as CT or MR venography. The GDG prioritised this recommendation as a key priority for implementation. They considered that it has a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes patient choice, promotes equalities and means patients reach critical points in the care pathway more quickly.

Recommendations	**4. Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score a D-dimer test and if the result is positive offer *either*:** • **a proximal leg vein ultrasound scan carried out within 4 hours of being requested *or*** • **an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.**
Relative values of different outcomes	The GDG considered the avoidance of undiagnosed and untreated DVT to be the most important issue, followed by concerns about the number of additional diagnostic tests (which are non invasive, with few side effects) that patients receive. This recommendation is intended to follow up patients with the appropriate tests after the pre-probability testing with a DVT Wells score. The ability to correctly confirm DVT, initiate treatment for patients with DVT and sending patients without DVT home without further imaging or treatments are considered the most important outcomes. Both sensitivity and specificity are also important outcomes. In this situation, D-dimer was considered in the context of ruling out DVT. The sensitivity and the negative predictive values in the population of interest ("unlikely" DVT) are

Recommendations	**4. Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score a D-dimer test and if the result is positive offer *either*:** • **a proximal leg vein ultrasound scan carried out within 4 hours of being requested *or*** • **an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.**
	the most important outcomes. This ensures that no patients with DVT are wrongly excluded from further diagnosis and treatment for the ultrasound scans since it is used to both confirm and rule out DVT.
Trade off between clinical benefits and harms	As sensitivity increases (less patients with DVT missed), the proportion of patients with a false positive test may increase (more patients sent for unnecessary further investigations and treatments and this is an important strain on the NHS resources). **D-dimer** D-dimer tests have relatively high sensitivity but low specificity (false positive results common). When the sensitivity of a d-dimer test increase, its specificity decreases. To be useful in the diagnosis of DVT, a D-dimer test has high sensitivity and high negative value - fewer people with DVT will be missed. Therefore, a negative D-dimer may be useful in excluding DVT but a positive D-dimer is of no diagnostic value, it merely mandates further testing. Whilst a negative D-dimer test is good enough to exclude the diagnosis of DVT in a patient with an "unlikely" pre-test clinical probability it is not good enough in those with a "likely" pre-test probability. **Proximal leg vein ultrasound scan** Proximal leg vein ultrasound scans are used as confirmatory tests in this pathway. Therefore both sensitivity and specificity are important, in order to ensure all DVTs are detected, and patients without DVT are not given heparin. The GDG had recommended proximal leg vein ultrasound scans as the clinical importance of picking up extra calf vein blood clots by scanning the whole leg is uncertain. Moreover, the evidence review suggested that ultrasound scan of calf veins are not very sensitive in picking up calf vein DVT. A repeat proximal leg vein scan is recommended to ensure that any clots propagating to the proximal veins are not missed. It is important to follow the sequence recommended to minimise the unnecessary use of ultrasound scans so that patients who need these scans can access them as soon as possible. Patient can be at risk of deterioration or at risk of a PE If a quick confirmation scan is not available. That is why anticoagulants are recommended if there is a delay in getting access to a scan.
Economic considerations	Based on a decision model comparing different sequences of tests, after risk stratification with a DVT Wells score, offering an ultrasound scan is cost-effective in the high risk group or after a positive D-dimer test. According to this model, offering a D-dimer test to patients who had a negative ultrasound scan is cost-effective. The cost of performing a D-dimer test is relatively low (between £19 and £20). Above-knee ultrasound with a repeat if negative is more cost-effective than a single above-knee or full-leg ultrasound scan.

Recommendations	**4. Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score a D-dimer test and if the result is positive offer *either*:** • **a proximal leg vein ultrasound scan carried out within 4 hours of being requested *or*** • **an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.**
	The four-hour limit to the ultrasound scan was not based on economic evidence but on safety considerations. The model was conducted using a three-level DVT Wells score but based on other considerations on implementation the GDG decided to recommend a two-level DVT Wells score.
Quality of evidence	**D-dimer** The majority of the evidence base comes from a large meta-analysis which pooled 97 diagnostic studies. The pooled sensitivity is 90%, indicating that 90% of patients with DVT will be correctly picked up. However, the main limitation of this evidence is this is a form of "average" sensitivity of all D-dimer tests. The actual sensitivity of tests varies between about 80% to more than 90%, depending on the specific type of technology used in the tests. **Proximal leg vein ultrasound scan** There was quality of evidence ranged from very low to moderate for the various ultrasound strategies reviewed. These studies showed that ultrasound scans have high specificities, which makes them effective in confirming the presence of DVT. However, the sensitivity of the tests can vary a little between studies and average around 90%. The economic evidence has potentially serious limitations and partial applicability.
Other considerations	Proximal ultrasound will be used to confirm whether patients have DVT if they presented with DVT symptoms and accessed as "likely" risk of DVT using a two-level DVT Wells score. The GDG considered at length the implications of implementation and whether this affects current practice. The following factors were discussed and considered by GDG members: • It is important to diagnose and confirm DVT quickly. Treatment with LMWH exposes patients to side effects and is expensive (cost of drug and district nurse time). It is important not to put patients needlessly on LMWH. • It is necessary to find a safe and cost-effective strategy to identify which patients can be sent home safely (through DVT Wells score and D-dimer), and reduce the number of people referred for an ultrasound scan. • Access to ultrasound scan can be a problem, especially at weekends and outside normal working hours. Delays in accessing ultrasound scans are a potential problem and these delays need to be addressed and avoided. In situations where delay in access is unavoidable, strategies are required to ensure that patients are treated in the interim. • Therefore, while it is recognised that access to ultrasound scans can be a limitation, it was also agreed that this should not be a reason on its own to

Recommendations	**4. Offer patients in whom DVT is suspected and with an *unlikely* two-level DVT Wells score a D-dimer test and if the result is positive offer *either*:** • **a proximal leg vein ultrasound scan carried out within 4 hours of being requested *or*** • **an interim 24-hour dose of a parenteral anticoagulant (if a proximal leg vein ultrasound scan cannot be carried out within 4 hours) and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.**
	prevent recommending what is required in the best interest of patients, especially when this is a very cost effective strategy. The GDG had considered that since patients assessed as having a high risk of DVT will not be sent home even if a D-dimer is negative, it is best to prioritise sending this group of patients to ultrasound scans so that a diagnosis can be confirmed and treatment initiated promptly. In patients with a "likely" DVT Wells score, patients with a positive ultrasound scan have DVT confirmed and need to be treated immediately, while patients with a negative ultrasound scan are offered a D-dimer to double check that there is a low risk of DVT before being sent home. The GDG also discussed that ultrasound techniques have important limitations in visualising iliac vein thrombosis. The current clinical understanding is this technique may not be effective if the relatively unusual situation of isolated iliac vein thrombosis is suspected. If this is suspected (for example, from changes in blood flow in the femoral vein), the usual practice is to investigate with other imaging methods such as CT or MR venography. The GDG prioritised this recommendation as a key priority for implementation. They considered that it has a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes patient choice, promotes equalities and means patients reach critical points in the care pathway more quickly.

Recommendations	**5. Diagnose DVT and treat (see recommendations 16 to 27) patients with a positive proximal leg vein ultrasound scan.**
Relative values of different outcomes	The number of DVT cases correctly diagnosed (true positives) and the number of false positives (when treatment may be started incorrectly) are the most important outcomes. It is also important that patients start treatment as soon as the diagnosis is confirmed.
Trade off between clinical benefits and harms	Proximal leg vein ultrasound scans are used as confirmatory tests in this pathway. Evidence showed that based on the specificity of proximal leg vein ultrasound scan, this test is suitable for the purpose of confirming the presence of DVT. Both sensitivity and specificity are important in order to ensure all DVTs are detected and patients with DVT are treated. The GDG had recommended proximal leg vein ultrasound scans as the clinical importance of picking up extra calf blood clots through whole leg scan is uncertain.
Economic considerations	Based on a decision model comparing different sequences of tests, a strategy

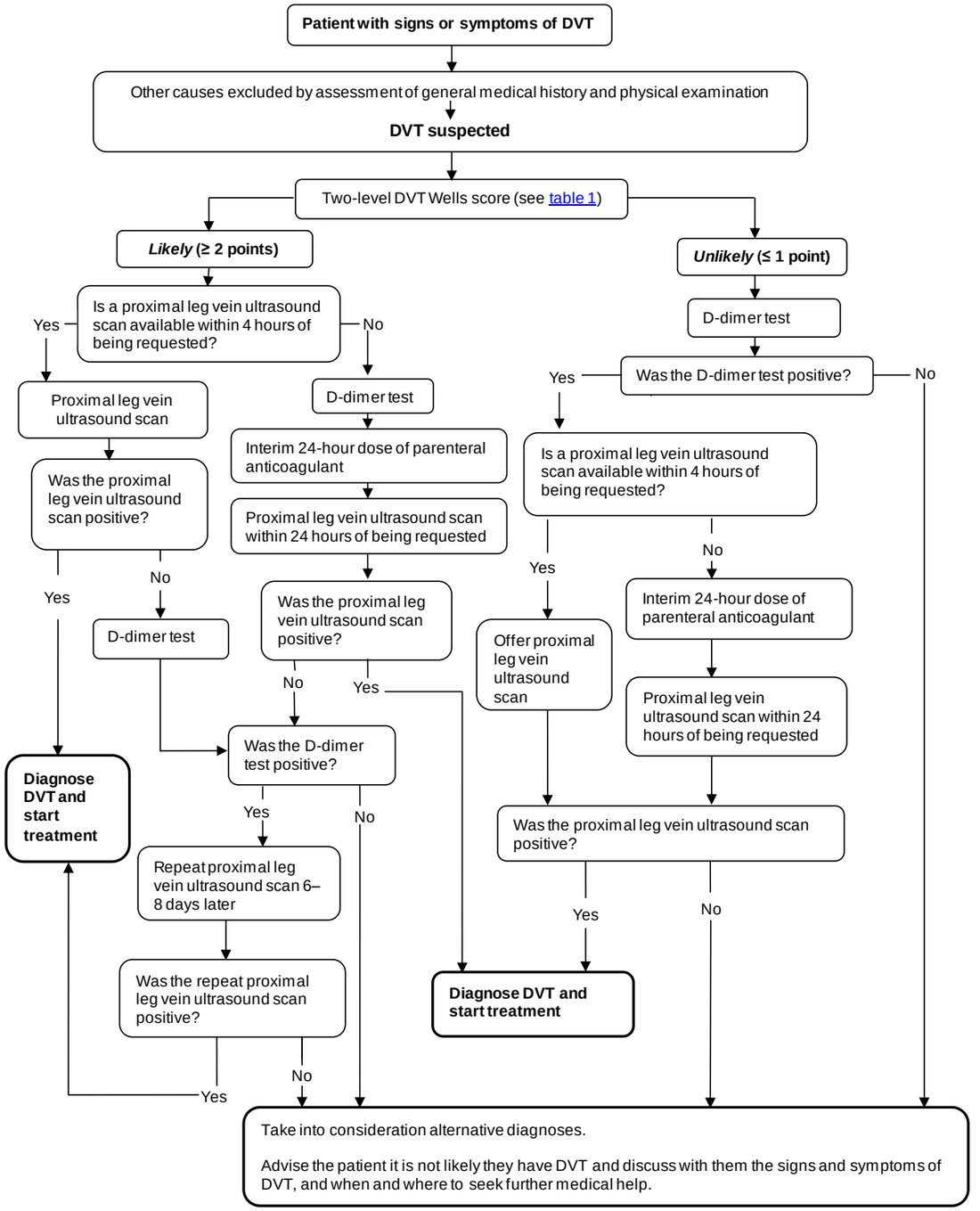
Recommendations	**5. Diagnose DVT and treat (see recommendations 16 to 27) patients with a positive proximal leg vein ultrasound scan.**
	where diagnosis of DVT is confirmed by ultrasound is cost-effective.
Quality of evidence	The quality of evidence ranged from very low to moderate for the various ultrasound strategies reviewed. These studies showed that ultrasound scans have high specificities, which makes them effective in confirming the presence of DVT. However, the sensitivity of the tests can vary a little between studies and average around 90%. The economic evidence has potentially serious limitations and partial applicability.
Other considerations	It is important to diagnose and confirm DVT quickly. Treatment with LMWH exposes patients to side effects and is expensive (cost of drug and district nurse time). It is important not to put patients needlessly on LMWH. The GDG also discussed that ultrasound techniques have important limitations in visualising iliac vein thrombosis. The current clinical understanding is this technique may not be effective if the relatively unusual situation of isolated iliac vein thrombosis is suspected. If this is suspected (for example, from changes in blood flow in the femoral vein), the usual practice is to investigate with other imaging methods such as CT or MR venography. See also recommendations on treatment of DVT.

Recommendations	**6. Take into consideration alternative diagnoses in patients with:** • **an *unlikely* two-level DVT Wells score *and*** - **a negative D-dimer test *or*** - **a positive D-dimer test and a negative proximal leg vein ultrasound scan.** • **a *likely* two level DVT Wells score *and*** - **a negative proximal leg vein ultrasound scan and a negative D-dimer test *or*** - **a repeat negative proximal leg vein ultrasound scan.** **Advise patients in these two groups that it is not likely they have DVT, and discuss with them the signs and symptoms of DVT and when and where to seek further medical help.**
Relative values of different outcomes	The number of DVT cases missed (false negatives) and the number of false positives (when treatment may be started incorrectly) are the most important outcomes. It is also important that patients are reassured that they do not have DVT, but have information about when to come back if they have more signs and/or symptoms of a possible DVT.
Trade off between clinical benefits and harms	The benefit to informing the patient that they are unlikely to have a DVT is that other diagnosis can then be considered and that no further investigation into a DVT is necessary. If no further tests are pursued, there is a small possibility that a DVT may be missed, but this possibility is minimised with the diagnostic strategy recommended: • There is a very low risk of DVT in patients with an “unlikely” DVT Wells score and negative D-dimer

Recommendations	**6. Take into consideration alternative diagnoses in patients with:** • **an *unlikely* two-level DVT Wells score *and*** - **a negative D-dimer test *or*** - **a positive D-dimer test and a negative proximal leg vein ultrasound scan.** • **a *likely* two level DVT Wells score *and*** - **a negative proximal leg vein ultrasound scan and a negative D-dimer test *or*** - **a repeat negative proximal leg vein ultrasound scan.** **Advise patients in these two groups that it is not likely they have DVT, and discuss with them the signs and symptoms of DVT and when and where to seek further medical help.**
	• There is a very low risk of DVT in patients with an "unlikely" DVT Wells score, positive D-dimer, and a negative proximal leg vein ultrasound scan. • There is a very low risk of DVT in patients with a "likely" DVT Wells score, a negative D-dimer, and a negative proximal leg vein ultrasound scan. • There is a very low risk of DVT in patients with a "likely" DVT Wells score, a negative proximal leg vein ultrasound scan, a positive D-dimer, and a repeat negative proximal leg vein ultrasound scan The risk of DVT for any of the above groups is very low; they either had a low pre-test probability and a negative result from a sensitive test, or had a higher pre-test probability but tested negative with two different high sensitivity tests. It is not beneficial to subject these patients to further tests because the probability of having missed a DVT is very low. In the unlikely event that these tests missed a DVT, patients need to know about the signs and symptoms of DVT and when or where to seek further help or advice. Therefore, this information should be given to all patients who presented with a suspected DVT.
Economic considerations	Based on a decision model comparing different sequences of tests, ruling out a diagnosis of DVT is cost-effective when a patient has: • an intermediate/low DVT Wells score and a negative D-dimer or • a high DVT Wells score but a negative ultrasound scan and a negative D-dimer
Quality of evidence	No specific clinical evidence review was conducted for this area. This recommendation is supported by GDG consensus and information by economic evidence. The economic evidence has potentially serious limitations and partial applicability.
Other considerations	D-dimer is a sensitive test that is useful in excluding DVT in combination with a DVT Wells score which stratified patients into the appropriate pre-test probability categories. The evidence review suggests that the risk of patients actually having DVT is low if their DVT Wells score is "unlikely" and a D-dimer test is negative test, and this strategy can potentially exclude a large proportion of patients presenting with suspected DVT. For patients with a "likely" DVT Wells score, but a negative ultrasound scan, a negative D-dimer test helps to further eliminate the possibility that the patient has a DVT.

Recommendations	**6. Take into consideration alternative diagnoses in patients with:** • **an *unlikely* two-level DVT Wells score *and*** - **a negative D-dimer test *or*** - **a positive D-dimer test and a negative proximal leg vein ultrasound scan.** • **a *likely* two level DVT Wells score *and*** - **a negative proximal leg vein ultrasound scan and a negative D-dimer test *or*** - **a repeat negative proximal leg vein ultrasound scan.** **Advise patients in these two groups that it is not likely they have DVT, and discuss with them the signs and symptoms of DVT and when and where to seek further medical help.**
	The GDG also discussed that ultrasound techniques have important limitations in visualising iliac vein thrombosis. The current clinical understanding is this technique may not be effective if the relatively unusual situation of isolated iliac vein thrombosis is suspected. If this is suspected (for example, from changes in blood flow in the femoral vein), the usual practice is to investigate with other imaging methods such as CT or MR venography.

Diagnosis of DVT algorithm



5.6 Summary of research recommendations

1. **What is the clinical and cost effectiveness of a whole-leg ultrasound scan compared with a proximal leg vein ultrasound scan in the diagnosis of acute DVT?**

The GDG noted that proximal leg vein ultrasound scans will not identify an isolated calf vein thrombus but that a repeat scan 1 week later will identify the clinically important thrombi that have extended. If a whole-leg scan is conducted initially, no repeat ultrasound at 1 week is required, but more patients may need anticoagulation therapy. More DVTs are identified by a whole-leg scan but this is more time consuming and the impact on patient outcomes is unknown. Whole-leg scans are also more difficult technically and are subject to variability because there are more veins within the calf and they are considerably smaller; therefore there is still a risk of missing a calf vein thrombus. Repeating the proximal leg ultrasound scan after 1 week necessitates two scans, which is also time-consuming. A randomised controlled trial (RCT) with cost-effectiveness analysis could answer the crucial question of whether full-leg ultrasound improves patient outcomes and allows for more effective use of NHS resources. Primary outcomes should include objectively confirmed 3-month incidence of symptomatic VTE in patients with an initially normal diagnostic work-up, mortality and major bleeding.

6 Diagnosis of pulmonary embolism

6.1 Introduction

Effective diagnosis is crucial as PE is a treatable condition and severe cases of PE can lead to collapse and / or sudden death. Some PEs are rapidly fatal, and in the majority of the fatal cases they are not clinically diagnosed prior to death. In patients where PE is diagnosed, the mortality rate is lower in those who are haemodynamically stable and higher in those who present in cardiorespiratory arrest. The outcome is dependent on the clot burden and the underlying cardiorespiratory function. Although DVT and PE are manifestations of the same disease process, mortality is significantly higher with PE. If left untreated, the prognosis for PE is poor. Even when treated, some patients develop chronic thromboembolic pulmonary hypertension due to fibrotic, occlusive organisation of thrombi/emboli and pulmonary vascular remodelling.

The symptoms and signs of PE are not specific and include dyspnoea, pleuritic chest pain (due to pleural irritation in pulmonary infarction), retrosternal chest pain (due to right ventricular ischaemia), cough and haemoptysis. In severe cases, the right ventricle fails leading to dizziness and/ or syncope. The signs include tachypnoea, tachycardia, hypoxia, pyrexia, elevated jugular venous pressure, a gallop rhythm, a widely split second heart sound, tricuspid regurgitant murmur, pleural rub, systemic hypotension and cardiogenic shock.

Studies of patients with suspected PE have reported different estimates of prevalence. Both under diagnosis and over diagnosis of PE carry substantial morbidity and mortality. Diagnosis is usually confirmed objectively by ventilation perfusion (V/Q) scan or CT pulmonary angiogram (CTPA). However, because of the cost of these modalities and the increasing number of negative tests, strategies have been developed which can exclude the diagnosis in some patients without the need for diagnostic imaging. These rely on the use of information from clinical history and examination (a pre-test probability assessment) and assays to detect D-dimers.

Accurate diagnosis to tailor management is crucial as treatment with anticoagulation has side-effects.

6.2 Clinical probability scores and D-dimers

Diagnosing PE is a diagnostic challenge because the symptoms and signs are common and not specific. The initial step for patients presenting with signs and symptoms of possible PE is to assess their likelihood of having a PE. It is important to adopt a strategy which can safely rule out the diagnosis of PE in a significant proportion of patients. Therefore, several clinical prediction scores incorporating predisposing factors, symptoms and clinical signs have been developed.

There are a number of clinical prediction pre-test probability scores which have been developed to assess the probability that a person has a PE based on their presenting signs, symptoms and history. These involve using a scoring systems and the resulting score is used to stratify patients into different levels of risk of having PE, for example, as ‘low’, ‘moderate’ or ‘high’ risk, or more recently as ‘likely’ or ‘unlikely’ to have a PE. A number of scores have been developed using different methods and have different types of validation studies. It is important to identify clinical scores with good validity and reliability as an initial pre-test probability scoring system to reliably group patients into different risks of PE. We have looked at some of the commonly used scores: Wells score (original and revised), Geneva score, (original and revised) and Charlotte rule. In this review, we investigated the effectiveness of these different scores (and scoring methods) in ruling out PE.

PE Wells score (original) - In 1998, Wells et al[264] developed a seven-component clinical prediction rule for PE. Points are given based on criteria in the history and examination including for example:

signs of DVT, tachycardia greater than 100 beats per minute, active cancer and recent immobilisation. This gives a possible score range of 0 to 12.5. A score of greater than 6 is classified as 'high risk' of PE; a score of 2 to 6 as 'intermediate risk' of PE; and a score less than 2 as 'low risk'.

PE Wells score (two-levels) - In 2000 the Wells score for PE was revised to create only two categories: "likely" (score greater than 4) and "unlikely" (score of 4 or less)[263] (Table 20).

Table 20: Two-level PE Wells score (from Wells et al (2000)[262] with permission from author)

Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate greater than 100 beats per minute	1.5
Immobilisation (for more than 3 days) or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical probability simplified score	
PE *likely*	More than 4 points
PE *unlikely*	4 points or less

Geneva score (original and revised) - The original Geneva score[266] is based on seven clinical factors and required interpretation of the findings on chest X-ray and arterial blood gases. The revised Geneva score[136] covers eight parameters in 3 clinical areas: risk factors, symptoms and clinical signs. Each of these is given 1 to 5 points accordingly. This gives a possible score range of 0 to 25. A score of 11 or higher is classified as 'high risk' of PE; a score of 4 to 10 as 'intermediate risk' and a score of 0 to 3 as 'low risk'.

Charlotte rule - Kline et al[127] developed the PE rule-out criteria [PERC], or Charlotte rule. Patients with suspected PE (based on empiric clinical assessment) are stratified into low-risk and high-risk (pre-test probability groups). Patients are classified as high risk if they have at least two of the following:

- Age greater than 50
- Heart rate greater than systolic blood pressure
- Surgery in the past month
- Unilateral leg swelling
- Haemoptysis
- Unexplained oxygen saturation less than 95% on room air.

In contrast to other investigators, Kline et al[127] did not find that either active cancer or a previous history of VTE were significantly associated with the risk of PE.

Additional diagnostic predictive value can be achieved by combining a clinical prediction score with D-dimer testing. D-dimer concentrations are elevated in an acute clot due to the resulting activation of fibrinolysis. The negative predictive value of D-dimer is high; however its specificity for VTE is poor.

6.2.1 In people with suspected PE, can we safely rule out further imaging based on clinical probability score and D-dimer assay?

See evidence tables in Appendix E.4.

6.2.1.1 Clinical evidence

Table 21: Clinical score and D-dimer – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Wells score (revised) [262] plus quantitative D-dimer (VIDAS D-dimer, Tinaquant, automated)						
Number of PE cases missed [4,78,233,249]	4	Cohorts	No serious limitations	No serious inconsistency	Serious indirectness (a)	No serious imprecision
Wells score (revised) [262] plus semi-quantitative/qualitative D-dimer (Simplify, SimpliRED)						
Number of PE cases missed [205]	1	Cohorts	Serious limitations (b)	No serious inconsistency	Serious indirectness (c)	No serious imprecision
Wells score (original) [264] plus semi-quantitative/qualitative D-dimer (Simplify, SimpliRED)						
Number of PE cases missed [128,263]	2	Cohorts	Serious limitations (c)	No serious inconsistency	Serious indirectness (c)	No serious imprecision
Geneva score (original) [266] plus quantitative D-dimer (VIDAS D-dimer, Tinaquant)						
Number of PE cases missed [8,191]	2	Cohorts	Very serious limitations (d)	No serious inconsistency	Serious indirectness (e)	No serious imprecision
Geneva score (revised)[136] plus quantitative D-dimer (VIDAS D-dimer, Tinaquant)						
Percentage of patients ruled out [203]	1	Cohorts	Serious limitations (f)	No serious inconsistency	Serious indirectness (f)	No serious imprecision
Charlotte rule [127] plus semiquantitative D-dimer						
Number of PE cases missed [128]	1	Cohorts	Serious limitations (c)	No serious inconsistency	Serious indirectness (c)	No serious imprecision

(a) One study [4] recruited less than 50% of patients screened. In two studies,[78,249] 2.4% and 10% of patients violated the protocol (had extra imaging).

(b) Patients were enrolled when presenting at the nuclear medicine department. Unclear whether this is consecutive patients presenting with symptoms. Less than 50% of screened patients enrolled.

(c) Screening and inclusion criteria unclear. Unclear what percentage of patients screened were enrolled. In one study [128], some clinicians may order imaging tests in negative D-dimer patients - unclear why or how many.

(d) Clinicians allowed to overrule the Geneva scoring classification (using "clinical judgement"), it is unclear how many cases were overruled, and what were the criteria for overruling (one study which was excluded reported up to about 40%)

(e) Unclear whether results are reproducible if applied to guideline populations.

(f) Clinicians allowed to overrule Geneva score rating – cases and criteria described. However percentage of PE cases missed using this method is not reported.

Table 22: Clinical scores and D-dimers – Clinical summary of findings

Score	D-dimer tests	Prevalence (%)	% ruled out by tests	Number of PE cases missed (FN), per 1000		Quality
				Per protocol	ITT	
Wells – revised	Quantitative	12.4 to 20.5	11.2to 51.2	0 to 1.9	0 to 13.3	MODERATE
Wells - revised	Semi-quantitative/ qualitative	8.5	17.6	0	0	LOW
Wells - original	Semi-quantitative/ qualitative	4.7 to 9.2	47.0 to 54	0 – 2.3	6.9 to 12.1	LOW
Geneva Original	Quantitative	20.8 to 25.8	20.1 to 30.7	0	0 to 8.6	VERY LOW
Geneva revised	Quantitative	20.8%	30.84%	NR	NR	LOW
Charlotte rule	Semi-quantitative/ qualitative	4.7	65.64%	0	10.6	LOW

6.2.1.2 Economic evidence

See section 6.5.

6.2.1.3 Evidence statements

Clinical

Four studies with 6122 people in a population with a prevalence of 12.4 to 20.5% of PE show that a PE Wells score (two-levels) and quantitative D dimer rule out 11.2 to 51.2% instances of PE in this population. There were 0 to 1.9 cases of PE missed per 1000 patients screened using this method. The worst case scenario, using ITT analysis which includes all missing data, shows that there were 0 to 13.3 cases of PE missed per 1000 patients screened using this method (MODERATE QUALITY).

One study with 399 people in a population with an 8.5% prevalence of PE shows that a PE Wells score (two-level) and semi-quantitative or qualitative D-dimer rule out 17.6% instances of PE in this population. The number of cases of PE missed per 1000 patients screened using this method was not available for this study (LOW QUALITY).

Two studies with 3248 people in a population with a prevalence of 4.7 to 9.2% of PE show that a PE Wells score (three-levels) and semi-quantitative or qualitative D-dimer rule out 47% to 54% instances of PE in this population. There were 0 cases of PE missed per 1000 patients screened using this method. The worst case scenario, using ITT analysis which includes all missing data, shows that there were 6.9 to 12.1 cases of PE missed per 1000 patients screened using this method (LOW QUALITY).

Two studies with 1361 people in a population with a prevalence of 20.8 to 25.8% of PE shows that a Geneva score (original) and quantitative D-dimer rule out 20.1 to 30.7% instances of PE in this population. There were 0 to 2.3 cases of PE missed per 1000 patients screened using this method. The worst case scenario, using ITT analysis which includes all missing data, shows that there were 0 to 8.6 cases of PE missed per 1000 patients screened using this method (VERY LOW QUALITY).

One study with 1819 people with a prevalence of 20.8% PE shows that a Geneva score (revised) and quantitative D-dimer rule out 30.8% instances of PE in this

population. The cases of PE missed per 1000 patients screened using this method was not reported (LOW QUALITY).

One study with 2302 people in a population with a prevalence of 4.7% PE shows that Charlotte rule and semi-quantitative or qualitative D-dimer rule out 65.64% instances of PE in this population. There were 0 cases of PE missed per 1000 patients screened using this method. The worst case scenario, using ITT analysis which includes all missing data, shows that there were 10.6 cases of PE missed per 1000 patients screened using this method (LOW QUALITY).

Economic

The most cost-effective strategy involves managing patients according to their two-level PE Wells score: if PE is likely (score of 5 points or more) offer a CTPA; if PE is unlikely (score 4 points or less) offer a D-dimer and a CTPA only if the D-dimer is positive. There is a high uncertainty as to whether adding a proximal ultrasound of the lower limbs in patients with a likely PE when the CTPA is negative is cost-effective. This evidence is directly applicable but it has potentially serious limitations.

6.3 Ventilation perfusion scans

A ventilation perfusion (V/Q) scan involves two parts, both of which require the use of radio-isotopes. The ventilation part involves a patient breathing the isotope, either in the form of a gas or in fine aerosol particles. The perfusion part involves giving the patient an intravenous injection of the isotope.

Images for both phases are acquired using a gamma camera that detects where the isotope in the gas/aerosol and in the intravenous injection have gone into the lungs. This allows the identification of areas that are ventilated but not perfused, which enhances the diagnostic accuracy of the test.

A relatively new advance in V/Q scanning is V/Q single photon emission computed tomography (V/Q SPECT). Here images are obtained in various planes by the gamma camera rotating round the patient and the information can then be manipulated to show 3-dimensional views or slices in any plane, making the test far more accurate.

The typical effective radiation dose associated with lung ventilation and lung perfusion scans are reported in Table 23 where they are compared with the radiation dose of a chest CT. These data are based on the Referral Guidelines issued by the Royal College of Radiologists.[208]

Table 23: Typical radiation doses from diagnostic procedures

Diagnostic test	Typical effective radiation dose (mSv)	Equivalent number of chest X-rays	Approximate equivalent period of natural background radiation[(a)]
Lung ventilation	0.3[(b)]	15	7 weeks
Lung perfusion	1	50	6 months
CT chest	8	400	3.6 years

(a) UK average background radiation=2.2 mSv per year.

(b) The radiation dose could vary between 0.1 and 0.6 mSv according to the ventilation agent used.

6.3.1 In people with suspected PE, what is the effectiveness of ventilation perfusion scans in ruling out PE?

See evidence tables in Appendix E.6.

6.3.1.1 Clinical evidence

For this clinical question several different types of study were identified as relevant to the clinical question.

One RCT was identified which compared V/Q scanning with CTPA[4]. See Table 24 and Table 25 respectively for quality assessment and clinical summary of findings.

Five diagnostic studies were identified for V/Q scans; one of these studies assessed the diagnostic accuracy of both V/Q planar lung scintigraphy and V/Q SPECT[89]. Table 26 and Table 27 contain the quality assessment and summary of findings for V/Q planar lung scintigraphy. The number of indeterminate or non-diagnostic patients was quite high in some of these studies, and this affects our interpretation of the sensitivity and specificity in these studies. Therefore, we have provided the details in Table 28.

Table 24: V/Q scans vs CTPA – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Mortality (among patients whom VTE was initially excluded) [(a) 4]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[(b)]
Symptomatic PE or proximal DVT events in VTE patients whom VTE was initially excluded[4]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Very serious imprecision[(c)]

(a) The study reported all cause mortality; it states that most mortality was due to complications of underlying malignancy.
(b) CI crosses MID points making the effect size uncertain.
(c) CI crossed both MID points making the effect size very uncertain.

Table 25: V/Q scans vs CTPA – Summary of findings

Outcome	CTPA	V/Q scan	Relative risk (95%) CI)	Absolute effect	Quality
Mortality (among patients whom VTE was initially excluded)	17/561 (3.03%)	30/611 (4.91%)	RR 0.62 (0.34 to 1.11)	19 fewer per 1000 (from 32 fewer to 5 more)	MODERATE
Symptomatic PE or proximal DVT events in VTE patients whom VTE was initially excluded	2/561 (0.36%)	6/611 (0.98%)	RR 0.36 (0.07 to 1.79)	6 fewer per 1000 (from 9 fewer to 8 more)	LOW

Table 26: V/Q scan (planar lung scintigraphy) – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Sensitivity, Specificity, Positive PPV and NPV [88,89,176,257,258]	5	Diagnostic studies	Very serious limitations [(a-c)]	Serious inconsistency [(d)]	No serious indirectness	No serious imprecision
3 month VTE rate	0	-	-	-	-	-
Radiation burden compared with V/Q	0	-	-	-	-	-
Mortality	0	-	-	-	-	-

(a) Very small sample size in four studies [88,89,176,258]. In one study [258] only 28/82 received V/Q scans.

(b) There serious limitation sin the interpretation of the sensitivity and specificity of results reported due to the relatively large number of non-diagnostic or indeterminate cases in some studies – these were frequently excluded from the analysis of sensitivity and specificity or not reported clearly. In one study, 89 41 patients were included in the study but five were indeterminable for final diagnosis (i.e. there was no reference available, due to suboptimal technical quality of the datasets;) however the non-diagnostic rate does not reflect this (0%). In the same paper89 the same five patients were included as non-diagnostic for V/Q SPECT, therefore the sensitivity and specificity was based on 36 patients .In one study[258] two patients with non-diagnostic scans (intermediate probability) were excluded. In one study88 there were 9 patients indeterminate with the pulmonary angiogram. 30 patients were indeterminate (non-diagnostic) for the V/Q scans, 12 had PE with pulmonary angiogram and 18 did not. The sensitivity and specificity are for those patients given a diagnostic label. Those with indeterminate probability (non-diagnostic) showed a single segmental mismatch (>75% seg); subsegmental defects with radiological collapse; multiple matched and mismatched abnormalities; widespread airways disease affecting >50% lung; all other perfusion defects including those associated with a radiological opacity. We have provided more details in Table 28.

(c) One study [257] showed the sensitivity and specificity from those with high, intermediate and low probability of having PE, this therefore included the non-diagnostic values. There were a large number of indeterminate cases. As we do not know where these indeterminate cases would lie it could mean that the sensitivity and specificity are higher than if the non-diagnostic cases had been included. We have provided more details in Table 28.

(d) There was variation in whether studies excluded non-diagnostic patients before assessing sensitivity and specificity.

Table 27: V/Q scan (planar lung scintigraphy) – Clinical summary of findings

Outcome / Test	Prevalence (%)	Non-diagnostic rate	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Quality
Ventilation perfusion scans (planar lung scintigraphy)	25 to 82.3	0 to 38.5%	41 to 100	72 to 97	76 to 100	50 to 94	VERY LOW

Table 28: V/Q scan (planar lung scintigraphy) – results from individual studies included in review

Study	Total patients	TP (c)	TN (c)	FP (c)	FN (c)	Non-diagnostic	Un-accounted	Sensitivity	Specificity
V/Q scan- planar lung scintigraphy									
Gray (1990)[88(a)]	78	15	32	1	0	30	-	1.00 [0.78, 1.00]	0.97 [0.84, 1.00]
Gutte (2010)[89(a)]	41	7	18	7	4	5	-	0.64 [0.31, 0.89]	0.72 [0.51, 0.88]
Ohno (2004)[176]	48	8	28	8	4	0	-	0.67 [0.35, 0.90]	0.78 [0.61, 0.90]
Wang (2009)[258 (a)]	28	11	13	1	1	2	-	0.92 [0.62, 1.00]	0.93 [0.66, 1.00]
Vreim (1990)[257] (H)[(a,b)]	731	102	466	14	149	-	-	0.41 [0.35, 0.47]	0.97 [0.95, 0.98]
Vreim (1990)[257] (H/I) [(a,b)]	731	207	249	231	44	-	-	0.82 [0.77, 0.87]	0.52 [0.47, 0.56]
Vreim (1990)[257] (H/I/L) [(a,b)]	731	246	50	430	5	-	-	0.98 [0.95, 0.99]	0.10 [0.08, 0.14]
Vreim (1990)[257 (b)] exclude non diagnostic	731	-	-	-	-	364	-	-	-
V/Q SPECT									
Gutte (2001)[89](SPECT)[(a),]	41	10	20	3	0	5	3	1.00 [0.69, 1.00]	0.87 [0.66, 0.97]

(a) Table shows the valued as reported in the studies. Please see footnotes on Table 26 and Table 29 for study limitations.
(b) Vreim (1990) [257] divided the population into high, intermediate and low risk of PE.
(c) TP= true positive, TN = true negative, FP =false positive, FN = false negative.

Table 29: Ventilation perfusion scans (V/Q SPECT) – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Sensitivity, Specificity , NPV, and PPV [89]	1	Diagnostic studies	Very serious limitations (a-e)	No serious inconsistency	No serious indirectness	No serious imprecision
3 month VTE rate	0	-	-	-	-	-
Radiation burden compared with V/Q	0	-	-	-	-	-
Mortality	0	-	-	-	-	-

(a) One study[89] had 2 people assessing the MDCT angiography, with 8 and 15 years of experience and only one person assessing the V/Q SPECT with 7 years of experience.

(b) Five patients were indeterminable as there was no reference available, due to the suboptimal technical quality of the dataset. The presence of indeterminate cases can make the sensitivity and specificity appear falsely elevated.

(c) There were three participants who were not included in the analysis and were not accounted for. Therefore the sensitivity and specificity are based on 33 patients.

(d) 41 patients were scanned but 3 patients were missing without details of why they were not included.

(e) Very small sample size.

Table 30: Ventilation perfusion scans (V/Q SPECT) – Clinical summary of findings

Outcome Test	Prevalence (%)	Non-diagnostic rate (%)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Quality
V/Q SPECT	31%	8	100%	87%	100%	77%	Very low

6.3.1.2 Evidence statements

Clinical

V/Q scans vs CTPA

One study with 1417 patients showed that there was a decrease in mortality in patients who had received CTPA scans compared to V/Q scans amongst patients who had initially been excluded; this may be of clinical importance, but there is a lot of uncertainty (MODERATE QUALITY).

One study with 1417 patients showed that it is very uncertain whether there is a clinically important difference in symptomatic PE or proximal DVT events in VTE patients whom had initially been excluded (LOW QUALITY).

V/Q scans (planar lung scintigraphy)

Five studies involving 1142 patients showed that sensitivity and specificity for planar lung scintigraphy ranged from 41 to 100% and 72 to 97% respectively. This means that 0 to 59 out of 100 patients with PE will be missed with planar lung scintigraphy. The specificity suggests that 3 to 28 out of 100 people without PE will be identified as having the condition. The included studies report a range of values for the specificity and sensitivity of ventilation perfusion scans; this means that there is variation in how good these scans are at diagnosing PE in patients. The included studies also vary with respect to whether indeterminate cases were included; where indeterminate cases are excluded the sensitivity and specificity of the diagnostic test could be overestimated, making it appear more effective (VERY LOW QUALITY).

V/Q (SPECT)

One small study with 41 patients showed sensitivity and specificity of V/Q (SPECT) to be calculated as 100% and 87% respectively. For the purposes of ruling out PE this suggests that no patients with PE will be missed when using V/Q (SPECT). The specificity suggests that 13 out of 100 people without PE will be identified as having the condition. However there is a lot of uncertainty surrounding this outcome as the figures calculated for sensitivity and specificity are likely to be overestimated as they did not take account of indeterminate cases (VERY LOW QUALITY).

Economic — The most cost-effective strategy involves managing patients according to their two-level PE Wells score: if PE is likely offer a CTPA; if PE is unlikely offer a D-dimer and a CTPA only if the D-dimer is positive. There is a high uncertainty as to whether adding a proximal ultrasound of the lower limbs in patients with a likely PE when the CTPA is negative is cost-effective. Strategies involving ventilation perfusion scan were not cost-effective in the base case. This evidence is directly applicable but it has potentially serious limitations.

6.4 Computed tomography (CT) scans

CT pulmonary angiography (CTPA) is performed by giving the patient a bolus of an intravenous contrast agent and then, when the contrast has reached the pulmonary arteries, CT of the chest is performed.

This allows the pulmonary arteries to be examined and enables the detection of pulmonary emboli (down to the subsegmental branches).

One advantage of CT is that it also looks at all of the other structures within the chest including whether there is evidence of right ventricular dilatation which has prognostic implications and can identify other causes for the patient's symptoms. The important disadvantage is that it gives the patient a much larger radiation dose compared to V/Q SPECT, hence increasing the life time risk of cancer.

Multidetector CT is performed with acquisition of 0.5- or 1-mm sections (depending on the weight of the patient) of the entire chest. Acquisitions are done during a single breath-hold lasting 10 to 12 seconds or less. Eighty to 100 mL of contrast agent is injected in the antecubital vein at an injection rate of 4.0 mL/sec. Acquisition of the static pulmonary angiography scan is started after automated detection of contrast agent (identified by enhancement) in the pulmonary trunk. A threshold rise of 100 Hounsfield units is usually selected for starting the acquisition.

The typical effective radiation dose associated with a CT scan is reported in Table 23 where it is compared with the radiation dose of lung ventilation and lung perfusion scans. These data are based on the Referral Guidelines issued by the Royal College of Radiologists.[208]

6.4.1 In people with suspected PE, what it is the effectiveness of CT scans in ruling out PE?

See evidence tables in Appendix E.5.

6.4.1.1 Clinical evidence

Table 31: CTPA – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Sensitivity, specificityPPV and NPV[25,36,174,176,199,201,209,231,267]	9	Diagnostic	Serious limitations (a)	No serious inconsistency	Serious indirectness (b)	Serious imprecision (c)
3 month VTE rate	0	-	-	-	-	-
Radiation burden compared with V/Q	0	-	-	-	-	-
Mortality	0	-	-	-	-	-

(a) Up to 50% of the studies were unclear regarding when CT and PA were performed and if the tests were carried out as close together as possible.

(b) The scan technology and protocols for over 50% of the included studies are out of date and therefore have limited applicability to current practice.

(c) The relatively low sample size gives wide CIs around the estimate of effect. This makes it difficult to know the true effect size for this outcome.

Table 32: CTPA – Clinical summary of findings

Outcome Test	Prevalence	Non- diagnostic rate (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Quality
CTPA	62/157 (39%) (a)	4 (a)	80 – 100	78 – 100	69 – 100	70- 100	VERY LOW

(a) Only reported by one study [199]

6.4.1.2 Economic evidence

See section 6.5.

6.4.1.3 Evidence statements

Clinical — Nine studies with 648 patients showed a sensitivity of 80 to 100% and a specificity of 78 to 100%. For the purposes of ruling out PE this suggests that 0 to 20 patients with PE will be missed when using CTPA. The specificity suggests that 0 TO 22 out of 100 people without PE will be identified as having the condition (VERY LOW QUALITY).

Economic — The most cost-effective strategy involves managing patients according to their two-level PE Wells score: if PE is likely offer a CTPA; if PE is unlikely offer a D-dimer and a CTPA only if the D-dimer is positive. There is a high uncertainty whether adding a proximal ultrasound of the lower limbs in patients with a likely PE when the CTPA is negative, is cost-effective. This evidence is directly applicable but it has potentially serious limitations.

6.5 Economic evidence

Eighteen studies[58,60,92,98,101,105,135,137,163,178,180,183,189,190,204,248,250,251] were found that compared different strategies for diagnosing PE. However, none of the studies fully met our quality and applicability criteria as the majority of the identified studies did not report QALYs. The only studies[60,204] reporting QALYs were partially applicable to the UK NHS setting and had additional limitations. It was thus decided to build an original economic model to compare the possible strategies available to diagnose PE. See the cost- effectiveness analysis in Appendix H for further details.

Health economic modelling

a) Model overview/Methods

Eighteen diagnostic pathways were compared in the model (

Table 33). These were based on different combinations of the following tests: Wells score, D-dimer, CT, V/Q scan (SPECT in the base case, planar in a sensitivity analysis), and proximal ultrasound of the lower limbs.

Table 33 - Diagnostic pathways compared in the model

Strategy	Summary of strategy	Likely PE on CS	Unlikely PE on CS
1	CTPA all	CTPA all	
2	V/Q all	V/Q, +CTPA if non-diagnostic	
3	CS ± DDi ± CTPA	CTPA	DDi, +CTPA if DDi +ve
4	CS ± DDi ± CTPA ± V/Q	CTPA, +V/Q if CTPA –ve, +US if V/Q non-diagnostic	DDi +CTPA if DDi +ve
5	CS ± CTPA ± V/Q	CTPA +V/Q if CTPA –ve, +US if V/Q non-diagnostic	CTPA
6	CS ± DDi ± V/Q ± CTPA	V/Q +CTPA if V/Q non-diagnostic	DDi +V/Q if DDi +ve, CTPA if V/Q non-diagnostic
7	CS ± DDi ± V/Q ± CTPA	V/Q + CTPA if V/Q non-diagnostic	DDi + V/Q if DDi +ve, CTPA if V/Q non-diagnostic or -ve
8	CS ± DDi ± V/Q ± CTPA	V/Q + CTPA if V/Q –ve or non-diagnostic	DDi + V/Q if DDi +ve, CTPA if V/Q non-diagnostic
9	CS ± DDi ± V/Q ± CTPA	V/Q + CTPA if V/Q –ve or non-diagnostic	DDi + V/Q if DDi +ve, CTPA if V/Q non-diagnostic or -ve
10	V/Q ± CTPA	V/Q + CTPA when V/Q non -diagnostic	CTPA
11	CTPA ± US	CTPA + US if CTPA -ve	
12	V/Q (US)	V/Q + CTPA if non-diagnostic + US if CTPA-ve	
13	CS ± DDi ± CTPA± US	CTPA + US if CTPA -ve	DDi + CTPA if DDi +ve
14	CS ± DDi ± V/Q ± CTPA	V/Q + CTPA if V/Q non-diagnostic, US if CTPA -ve	DDi + V/Q if DDi +ve, CTPA if V/Q non-diagnostic
15	CS ± DDi ± V/Q ± CTPA	V/Q + CTPA if V/Q non-diagnostic, US if CTPA -ve	DDi + V/Q if DDi +ve, CTPA if V/Q non-diagnostic or –ve
16	CS ± DDi ± V/Q ± CTPA	V/Q + CTPA if V/Q –ve or non-diagnostic, US if CTPA -ve	DDi + V/Q if DDi +ve, CTPA if V/Q non-diagnostic
17	CS ± DDi ± V/Q ± CTPA	V/Q + CTPA if V/Q –ve or non-diagnostic, US if CTPA -ve	DDi + V/Q, CTPA if V/Q non-diagnostic or –ve
18	V/Q ± CTPA	V/Q + CTPA when V/Q non –	CTPA

Strategy	Summary of strategy	Likely PE on CS	Unlikely PE on CS
		diagnostic, US if CTPA -ve	

DDi = D-dimer

The economic evaluation was a cost-utility analysis, where lifetime costs and quality-adjusted life-years (QALYs) were considered from a UK NHS and personal social services perspective.

In the decision model, each arm of the tree ends up in a Markov model defined by the diagnostic outcome (true positive, true negative, false positive, false negative). The decision tree part of the model influences results by determining the total cost of tests and the proportion of patients being in one of the four possible diagnostic categories at termination: true positive (TP), false negative (FN), false positive (FP), true negative (TN). Lifelong outcomes (costs, mortality and quality of life as determined by treatment status and presence of PE) are calculated for the diagnostic categories.

Factors that have an impact on the overall costs and health benefits are the types of tests performed in the pathway, including their accuracy, the 3-month mortality from PE which depends on whether the patient is promptly treated, and the adverse effects of treatment (major bleeding which might result in stroke in some cases).

The model relies on some assumptions: the long-term mortality rate (i.e. beyond three months) in patients who had a PE is the same as in the general population (unless a stroke occurred); mortality after the first three months does not depend on whether PE is treated or not; the sensitivity and specificity of tests do not depend on prevalence of PE and are independent from previous tests performed. In addition, the model does not account for the increase risk of cancer due to the different levels of radiation exposure associated with tests.

The accuracy of diagnostic tests was based on our clinical review of diagnosis of PE (see 6.2.1.1, 6.3.1.1, 6.4.1.1) and for the ultrasound test it was based on the HTA model[85] (see 5.4.1.2).

b) Results

Most of the strategies were both less effective and more costly than at least one of the others in the base case deterministic and probabilistic analysis.

After taking into account simple dominance or extended dominance, three strategies were left to compare incrementally:

Strategy 3: Clinical score followed by CTPA if PE is 'likely' or by D-dimer test if PE is 'unlikely'. If the D-dimer test is abnormal, this is followed by a CTPA, if it is normal an alternative diagnosis should be considered. If undergoing CTPA, patients are managed according to the results of this test.

Strategy 13: Clinical score followed by CTPA if PE is 'likely' or by D-dimer test if PE is 'unlikely'. If undergoing CTPA, patients are treated if this test is positive; they undergo an US if the CTPA is negative and then are treated according to the results of the US. In patients with an unlikely Wells score, if the D-dimer test is abnormal, this is followed by a CTPA; if it is normal an alternative diagnosis should be considered.

Strategy 14: Clinical score followed by V/Q if PE is 'likely' or by D-dimer test if PE is 'unlikely'. If the D-dimer test is abnormal, this is followed by a V/Q, if it is normal an alternative diagnosis should be considered. In case of a non-diagnostic V/Q scan, a CTPA is performed. If the CTPA is negative but PE is likely, a proximal ultrasound is added.

The results of the probabilistic analysis are reported in Table 34. Adopting the NICE threshold of £20,000/QALY, in the base case strategy 13 is the optimal strategy. In fact, it is the strategy which provides the highest net benefit among the non-dominated options. Compared to strategy 3, it is more costly but also more effective and the ICER (£14,286/QALY) is below the NICE willingness-to-

pay threshold. On the other hand, strategy 14 is again more costly and more effective but in this case the ICER (£29,429/QALY) is above the NICE willingness-to-pay threshold, which means the increment in effectiveness obtained with strategy 14 does not justify the increment in cost.

Table 34: Results of incremental probabilistic analysis of non-dominated options using the NICE threshold of £20,000/QALY

Strategy	Mean cost per patient (£)	Mean QALYs per patient	ICER (£/QALY) (vs. previous strategy)	Net Benefit	Rank
Strategy 3	226	13.8477		276,728	2
Strategy 13	246	13.8491	14,286	276,737	1
Strategy 14	349	13.8526	29,429	276,703	3

A series of deterministic sensitivity analyses were conducted; overall results were robust to changes in some parameters (probability of major bleeding, accuracy of CS and D-dimer, stroke outcomes, use of V/Q planar, ultrasound scan in one leg) but they were sensitive to others (accuracy of CTPA, mortality from PE, prevalence of PE).

The model has some limitations: it is based on some assumptions (the accuracy of tests do not depend on the previous tests performed, the mortality after the first three months is the same as in the general population and does not depend on whether the PE was treated or untreated); it does not consider adverse effects of diagnostic tests such as the radiation exposure due to CTPA which may increase the likelihood of cancer; accuracy data are based on single studies and the accuracy of ultrasound is based on a meta-analysis of studies evaluating the test for the diagnosis of DVT.

As we have not incorporated the risk from the radiation exposure with CTPA, in patients at increased risk of cancer a strategy based on V/Q may be a better alternative to strategy 13 in our analysis.

6.6 Recommendations and link to evidence

Recommendations	**7. If a patient presents with signs or symptoms of PE, carry out an assessment of their general medical history, a physical examination and a chest X-ray to exclude other causes.**
Relative values of different outcomes	This recommendation helps to ensure that alternative diagnosis or causes of the signs and symptoms are fully investigated and have not been missed
Trade off between clinical benefits and harms	Assessing the general medical history and physical examination does not present any harm to the patient and may pick up or exclude other possible causes for the patient's symptoms. Completing this step of the diagnosis is crucial, as it will direct the consecutive diagnostic pathway to be undertaken for the patient. Ruling out alternative diagnosis is an item on the two-level PE Wells score. Performing this step correctly is crucial in the appropriate use of the two-level PE Wells Score and pre-test probability scoring.
Economic considerations	The assessment of the general medical history and the physical examination are associated with some increase in the clinician's time but they are not expected to increase costs considerably. Chest X-ray is associated with additional costs but they are likely to be offset by the advantages when ruling out other diagnoses and consequently avoiding further more costly tests and radiation exposure.
Quality of evidence	This is a supporting recommendation and we did not look at the evidence. This recommendation is based on GDG consensus.
Other considerations	Chest X-ray could help to detect other conditions such as pneumothorax, consolidation, and pleural effusion.

Recommendations	8. If PE is suspected, use the two-level PE Wells score (see Table 20) to estimate the clinical probability of PE.
Relative values of different outcomes	The effectiveness of using a strategy combining clinical probability scores and a simple test such as D-dimer to safely rule out PE was considered as the most important issue. This is measured as the number of PE cases missed. Another important consideration is the proportion of people presenting with PE that can be safely ruled out.
Trade off between clinical benefits and harms	There is a trade off between giving additional unnecessary tests and missing cases of PE. Using a clinical prediction rule is the first step in the diagnosis of PE, by categorising patients presenting with suspected PE into different pre-test probabilities. Establishing groups with different pre-tests risks helps determine which tests would be appropriate for the purpose of ruling out PE or confirming it. The GDG considered the clinical impact of minimising missed cases of PE was outweighed by the time required to use a validated score. In addition, when followed by a D-dimer test in the group with "unlikely" PE, the evidence reviewed showed that the number of PE cases missed is very low using a combination of clinical prediction scores such as a PE Wells score and D-dimer test.
Economic considerations	Offering patients with suspected PE a two-level PE Wells score is part of the most cost-effective strategy. Calculating a two-level PE Wells score is associated with low costs while it is helpful to rule out PE together with a D-dimer test; it also helps avoid further more costly tests and radiation exposure.
Quality of evidence	The review focused on the numbers of PE missed for patients who had used a pre-test probability scoring system, followed up by D-dimer test to rule out PE. Studies which combined clinical prediction scores and D-dimer tests were found for the PE Wells score (three-level and two –level), Geneva (original and revised score) and Charlotte criteria. These studies showed that when used with a sensitive quantitative D-dimer test, these scores rarely missed any patients with PE. There were important limitations in studies using the Geneva scoring system, where clinicians were allowed to override the clinical rules – it was unclear how many patients required an "overrule" in those studies, making it difficult to estimate the performance of this score if the scoring system was strictly followed. The economic evidence has potentially serious limitations and direct applicability.
Other considerations	The use of clinical scores is considered a starting point and would be used in conjunction with other tests. Among the clinical scores, the Wells score was chosen because it safely ruled out PE when used in combination with sensitive D-dimer tests. The GDG decided to recommend the newer version of the PE Wells score (two-level, which categorise into "likely"/"unlikely") because it is easier to use (less chance of confusion about what to do with the "moderate" group in the old system) and it has also been well validated. Due to the weight of one subjective item in the two-level PE Wells score

Recommendations	**8. If PE is suspected, use the two-level PE Wells score (see Table 20) to estimate the clinical probability of PE.**
	("alternative diagnosis less likely than PE" – 3 points allocated), the experience and expertise of the person doing the scoring is an important consideration which could determine the effectiveness of the pre-test probability scoring system. It is important to emphasise that none of the pre-test probability scores reviewed could safely rule out PE when used alone. To safely rule out PE, an "unlikely" pre-test probability score should be followed with a D-dimer test of adequate sensitivity.

Recommendations	**9. Offer patients in whom PE is suspected and with a *likely* two-level PE Wells score *either*:** • **an immediate computed tomography pulmonary angiogram (CTPA) *or*** • **immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.** **Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected.**
Relative values of different outcomes	The most important outcome for this recommendation is the number of PE missed. This is balanced against minimising the number of patients receiving unnecessary imaging or anticoagulation treatments. **CTPA** Both sensitivity and specificity are important outcomes. In this situation, CTPA was considered in the context of confirming or ruling out PE. **Proximal ultrasound** The most important outcome was the identification of people with proximal DVT. Sensitivity was considered an important outcome so that a potential DVT is not missed.
Trade off between clinical benefits and harms	There is a trade off between missed PE cases and wrongly diagnosing and starting anticoagulation unnecessarily in someone who has neither a PE nor DVT. The diagnostic algorithm tries to achieve this balance, without subjecting patients to too many tests, especially when some tests, such as CTPA exposes patients to radiation. A single dose of parenteral anticoagulant is likely to have an overall benefit to patients who are waiting for diagnostic imaging to exclude a PE. Given that PE is potentially life threatening, the potential harms from a dose of a parenteral anticoagulant is less than the potential harms from delay of treatment. **CTPA** As sensitivity increases and specificity decreases (less patients with PE missed), the proportion of patients with a false positive test may increase (more patients commenced on unnecessary anticoagulant treatment). In the context of PE where the consequences of missing a diagnosis is severe, the GDG considered the risk of having an untreated PE to be more important that the risk of being given unnecessary anticoagulation treatment. Unnecessary radiation exposure was also considered. Chest CT is

Recommendations	**9. Offer patients in whom PE is suspected and with a *likely* two-level PE Wells score *either*:** • **an immediate computed tomography pulmonary angiogram (CTPA) *or*** • **immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.** **Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected.**
	approximately equivalent to 3.6 years of natural background radiation (UK average 2.2 mSv per year taken from referral guideline from the Royal College of Radiologists)[208]. **Ultrasound scan** CTPA is a sensitive test and patients with PE are unlikely to be missed. However, if CTPA is negative in a patient with suspected DVT, a proximal leg vein ultrasound scan should be offered so that the patient can get treated.
Economic considerations	**CTPA** Offering a CT scan to people with suspected PE and a 'likely' two level PE Wells score is part of the most cost-effective strategy. This test is associated with some cost but it is helpful to select the patients who need treatment. **Ultrasound scan** Offering a proximal compression ultrasound scan if the CT is negative was cost-effective in the base case scenario in the model developed. However, the results of the probabilistic analysis showed a great uncertainty over the cost-effectiveness of adding this test to the diagnostic pathway after a negative CT in patients with a likely PE. The GDG decided to recommend anticoagulation if diagnosis of PE cannot be confirmed immediately based on safety reasons; no economic evidence was considered to inform this recommendation.
Quality of evidence	**CTPA** The overall quality of evidence from the studies included in the review assessing the utility of CTPA in PE was very low. The GDG considered that the studies included in this review were relatively old, as was the technology used in the studies; therefore their applicability to current clinical practice was limited. **Ultrasound scan** The overall quality of evidence for ultrasound scans is low or moderate. The economic evidence has potentially serious limitations and direct applicability. There was no clinical or economic evidence review regarding the use of anticoagulants while waiting for imaging in patients with "likely" probability of PE. This is the recommendation made based on GDG consensus.
Other considerations	**CTPA** V/Q scan is a possible alternative to CTPA in patients with concerns about the level of radiation and adverse effects from contrast media (e.g. renal impairment and contrast media allergy). See recommendation 11. In addition,

Recommendations	**9. Offer patients in whom PE is suspected and with a *likely* two-level PE Wells score *either*:** • **an immediate computed tomography pulmonary angiogram (CTPA) *or*** • **immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.** **Consider a proximal leg vein ultrasound scan if the CTPA is negative and DVT is suspected.**
	people with claustrophobia may find the process of CTPA difficult. However, CTPA offers other advantages as well as being more sensitive and specific. The imaging also allows the observation of the following: • Secondary effects including right heart dysfunction/dilatation which has prognostic implications for risk of mortality in PE patients • Detection of other abnormalities in the chest area (the expert adviser to the GDG pointed out that CTPA may have an advantage in patients who are more than 50 years of age, who are also at an increased risk of cancer and more likely to have other abnormalities) If the CTPA is not available immediately, patients with a suspected PE should commence anticoagulation. **Proximal leg vein ultrasound scan** The GDG considered the following factors: • In patients where CTPA is negative, but there is a clinical suspicion of DVT, it is important to diagnose and confirm DVT quickly. • Ultrasound scan is a limited resource, and access can be a problem, especially at weekends or in more rural areas. Delays in accessing ultrasound scans are a potential problem and these need to be addressed and avoided. In situations where a delay in access is unavoidable, strategies are required to ensure that patients are treated. The GDG considered at length the implications of implementation and whether this affects current practice. The following factors were discussed and considered by GDG members: • It is important to diagnose and confirm PE quickly. Access to CTPA is usually unproblematic; however in situations where delay in access is unavoidable, strategies are required to ensure that patients are treated. The GDG discussed that putting patients on LMWH is expensive and may expose them to unnecessary side effects. However, untreated PE has an important risk of mortality. If a patient has a "likely" probability of PE, treatment may be started while waiting for confirmation, and stopped if the scan result is negative. • It is important to find a safe and cost-effective strategy to identify which patients can be sent home safely (through the use of a PE Wells score and D-dimer), and reduce the number of people who get referred for a CTPA. The GDG have prioritised this recommendation as a key priority for implementation. They considered that it has a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes equalities and means patients reach critical points in the care pathway more quickly.

Recommendations	**10. Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score a D-dimer test and if the result is positive offer *either*:** • **an immediate CTPA *or*** • **immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.**
Relative values of different outcomes	The most important outcome for this recommendation is the number of PE missed. This is balanced against minimising the number of patients receiving unnecessary imaging or anticoagulation treatments. **D-dimer** Both sensitivity and specificity are important outcomes. D-dimer was considered in the context of ruling out PE and sensitivity and negative predictive values were the most important outcomes. These outcomes reflect the number of patients with PE who may be incorrectly excluded from further diagnosis and treatment. **CTPA** Both sensitivity and specificity are important outcomes. In this situation, CTPA was considered in the context of confirming or ruling out PE.
Trade off between clinical benefits and harms	There is a trade off between missed PE cases, and wrongly diagnosing and starting anticoagulation unnecessarily in someone who has neither a PE nor DVT. The diagnostic algorithm tries to achieve this balance, without subjecting patients to too many tests, especially when some tests, such as CTPA, expose patients to radiation. A single dose of parenteral anticoagulant is likely to have an overall benefit to patients who are waiting for diagnostic imaging to exclude a PE. Given that PE is potentially life threatening, the potential harms from a dose of a parenteral anticoagulant is less than the potential harms from delay of treatment. **D-dimer** D-dimer tests with higher sensitivity have lower specificity, and there is a trade off between these two outcomes. As sensitivity increases (less patients with PE missed) and specificity decreases, the number of patients with a false positive test may increase (more patients sent for unnecessary further investigations, potential radiation exposure and the anxiety associated with such tests). In the context of PE where the consequences of missing a diagnosis is severe, the GDG considered that avoiding having an undiagnosed and untreated PE was more important than being subjected to further investigations (which are non invasive, with little side effects) and being anxious about the condition. **CTPA** As sensitivity increases and specificity decreases (less patients with PE missed), the proportion of patients with a false positive test may increase (more patients commenced on unnecessary anticoagulant treatment). In the context of PE where the consequences of missing a diagnosis is severe, the GDG considered the risk of having an untreated PE to be more important that the risk of being given unnecessary anticoagulation treatment. Unnecessary radiation exposure was also considered. Chest CT is approximately equivalent to 3.6 years of natural background radiation (UK

Recommendations	**10. Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score a D-dimer test and if the result is positive offer *either*:** • **an immediate CTPA *or*** • **immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.**
	average 2.2 mSv per year taken from referral guideline from the Royal College of Radiologists).
Economic considerations	**D-dimer** Offering people with suspected PE and an "unlikely" PE Wells score, a D-dimer test is part of the most cost-effective strategy. D-dimer test is associated with low costs while it is helpful to rule out PE together with a two-level PE Wells score and avoids further more costly tests and radiation exposure. **CTPA** Offering a CT scan to people with suspected PE, an 'unlikely' PE Wells score and positive D-dimer test is part of the most cost-effective strategy. This test is associated with some cost but it is helpful to select the patients who need treatment. The GDG decided to recommend anticoagulation if diagnosis of PE cannot be confirmed immediately based on safety reasons; no economic evidence was considered to inform this recommendation.
Quality of evidence	**D-dimer** The review for D-dimer tests in PE patients focused on the numbers of PE missed for patients who had used a pre- test probability scoring system, followed by a D-dimer test to rule out PE, and it was consistently shown that the D-dimer tests in combination with a validated pre- test probability scoring system can safely rule out PE. **CTPA** The overall quality of evidence from the studies included in the review assessing the utility of CTPA in PE was very low. The GDG considered that the studies included in this review were relatively old, as was the technology used in the studies; therefore their applicability to current clinical practice was limited. The economic evidence has potentially serious limitations and direct applicability. There was no clinical evidence review regarding the use of anticoagulants while waiting for imaging in patients with "likely" probability of PE. This is the recommendation made based on GDG consensus.
Other considerations	**D-dimer** There are various D-dimer tests available, including point of care tests (POCTs) which can be done in the community, for example by a GP. The sensitivity of the assays chosen is very important as different tests have varying sensitivities. **CTPA** V/Q scan is a possible alternative to CTPA in patients with concerns about the

Recommendations	**10. Offer patients in whom PE is suspected and with an *unlikely* two-level PE Wells score a D-dimer test and if the result is positive offer *either*:** • **an immediate CTPA *or*** • **immediate interim parenteral anticoagulant therapy followed by a CTPA, if a CTPA cannot be carried out immediately.**
	level of radiation and adverse effects from contrast media (e.g. renal impairment and contrast media allergy). See recommendation 11. In addition, people with claustrophobia may find the process of CTPA difficult. However, CTPA offers other advantages as well as being more sensitive and specific. The imaging also allows the observation of the following: • Secondary effects including right heart dysfunction/dilatation which has prognostic implications for risk of mortality in PE patients • Detection of other abnormalities in the chest area (the expert adviser to the GDG pointed out that CTPA may have an advantage in patients who are more than 50 years of age, who are also at an increased risk of cancer and more likely to have other abnormalities) If the CTPA is not available immediately patients with a suspected PE should commence anticoagulation. The GDG considered at length the implications of implementation and whether this affects current practice. The following factors were discussed and considered by GDG members: • It is important to diagnose and confirm PE quickly. Access to CTPA is usually unproblematic; however in situations where delay in access is unavoidable, strategies are required to ensure that patients are treated. The GDG discussed that putting patients on LMWH is expensive and may expose them to unnecessary side effects. However, untreated PE has an important risk of mortality. If a patient has a "likely" probability of PE, treatment may be started while waiting for confirmation, and stopped if the scan result is negative. • It is important to find a safe and cost-effective strategy to identify which patients can be sent home safely (through the use of a PE Wells score and D-dimer), and reduce the number of people who get referred for a CTPA. The GDG have prioritised this recommendation as a key priority for implementation. They considered that it has a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes equalities and means patients reach critical points in the care pathway more quickly.

Recommendations	**11. For patients who have an allergy to contrast media, or who have renal impairment, or whose risk from irradiation is high:** • **Assess the suitability of a ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scan or, if a V/Q SPECT scan is not available, a V/Q planar scan, as an alternative to CTPA.** • **If offering a V/Q SPECT or planar scan that will not be available immediately, offer immediate interim parenteral anticoagulant therapy.**
Relative values of different outcomes	Both sensitivity and specificity are important outcomes. In this situation, V/Q SPECT was considered in the context of diagnosing or ruling out PE before starting treatment in patients who cannot have CTPA.
Trade off between clinical benefits and harms	Both sensitivity and specificity of the test are important, in order not to miss someone with PE or wrongly diagnose someone with PE and initiate anticoagulation treatment. Although CTPA has the advantage of being more sensitive and specific than V/Q scans which also have a higher non-diagnostic rate, V/Q scans may be the preferred option for some patients. The radiation exposure from V/Q scans is approximately equivalent to 8 months of natural background radiation (UK average 2.2 mSv per year), and significantly lower than CTPA scan[208]. Unlike CTPA, V/Q scans do not require the use of contrast media and should be offered to patients with a history of allergy to contrast media. This is also an option for patients at risk of further renal injury from contrast media e.g. patients with severe renal impairment. Therefore, for patients with additional risks from radiation, or adverse events of contrast media, V/Q scans offer an overall clinical benefit.
Economic considerations	Routinely offering people with suspected PE a V/Q scan was not shown to be cost-effective. In the economic model, all the strategies including a V/Q scan were both more costly and less effective than strategies involving a two-level PE Wells score, D-dimer and CTPA. However, it could be considered as an alternative to CTPA in some circumstances.
Quality of evidence	**CTPA** The overall quality of evidence from the studies included in the review assessing the utility of CTPA in PE was very low. The GDG considered that the studies included in this review were relatively old, as was the technology used in the studies; therefore their applicability to current clinical practice was limited. **V/Q scans** The majority of the studies looked at the use of planar lung scintingraphy. One study addressed the use of a newer technology, V/Q SPECT, however this was a very small study with serious limitations. The economic evidence has potentially serious limitations and direct applicability.
Other considerations	The GDG sought expert advice when making recommendations on the use of V/Q scans for the diagnosis of PE.

Recommendations	**11. For patients who have an allergy to contrast media, or who have renal impairment, or whose risk from irradiation is high:** • **Assess the suitability of a ventilation/perfusion single photon emission computed tomography (V/Q SPECT) scan or, if a V/Q SPECT scan is not available, a V/Q planar scan, as an alternative to CTPA.** • **If offering a V/Q SPECT or planar scan that will not be available immediately, offer immediate interim parenteral anticoagulant therapy.**
	Although diagnostic algorithms based on CTPA were found to be cost-effective compared to algorithms based on V/Q, the GDG discussed some situations where V/Q should be used instead of CTPA: when patients have contrast allergy, when patients have renal impairment, or when a CTPA is unavailable (for example, when a CT scanner is broken). The risk of cancer from the test radiation was also discussed. The lower radiation exposure obtained with V/Q compared to CTPA should be taken into account when deciding which test to use. Several factors (e.g. age) may affect the life time risk of cancer for a patient exposed to radiation from CTPA use. Based on the available evidence and on the expert advice, the GDG concluded that V/Q SPECT leads to better results compared to other types of V/Q (planar V/Q) as the non-diagnostic rate is lower with the former. However, it was recognised that V/Q SPECT might not be widely available in the NHS and in these circumstances, planar V/Q could be an acceptable alternative.

Recommendations	**12. Diagnose PE and treat (see recommendations 15 to 18 and 21 to 27) patients with a positive CTPA or in whom PE is identified with a V/Q SPECT or planar scan.**
Relative values of different outcomes	The number of PE cases correctly diagnosed (true positives) and the number of false positives (when treatment may be started incorrectly) are the most important outcomes. It is also important that patients start treatment as soon as the diagnosis is confirmed.
Trade off between clinical benefits and harms	There is a high risk of PE in patients with positive CTPA or V/Q. There is a trade-off between treating patients with PE who had a confirmatory CTPA or V/Q and the risk of unnecessarily treating patients without PE on the basis of a wrong interpretation of the CTPA or V/Q. Evidence showed that based on the specificity of CTPA and V/Q, these tests are suitable for the purpose of confirming the presence of PE. The results of these tests are reliable after the patients have gone through the whole diagnostic pathway which included two-level Wells score and in some cases D-dimer. In the context of PE where the consequences of missing a diagnosis is severe, the GDG considered the risk of having an untreated PE to be more important that the risk of being given unnecessary anticoagulation treatment.
Economic considerations	Diagnosing PE in people with a positive CTPA test was part of the most cost-effective strategy in the economic model developed. V/Q was an alternative option to confirm diagnosis of PE.
Quality of evidence	The review on CTPA showed that it is a sensitive and specific test, despite

	potential limitations in the evidence. The overall quality of evidence from the studies included in the review assessing the utility of CTPA in PE was very low. The GDG considered that the studies included in this review were relatively old, as was the technology used in the studies; therefore their applicability to current clinical practice was limited. The economic evidence has potentially serious limitations and direct applicability.
Other considerations	The GDG discussed that treatment is expensive and may expose patients to unnecessary side effects. However, untreated PE has an important risk of mortality and CTPA or V/Q scans can reliably detect patients with PE who require treatment. See also recommendations 15 to 18 on treatment for PE and 21 and 22 on PE diagnosis.

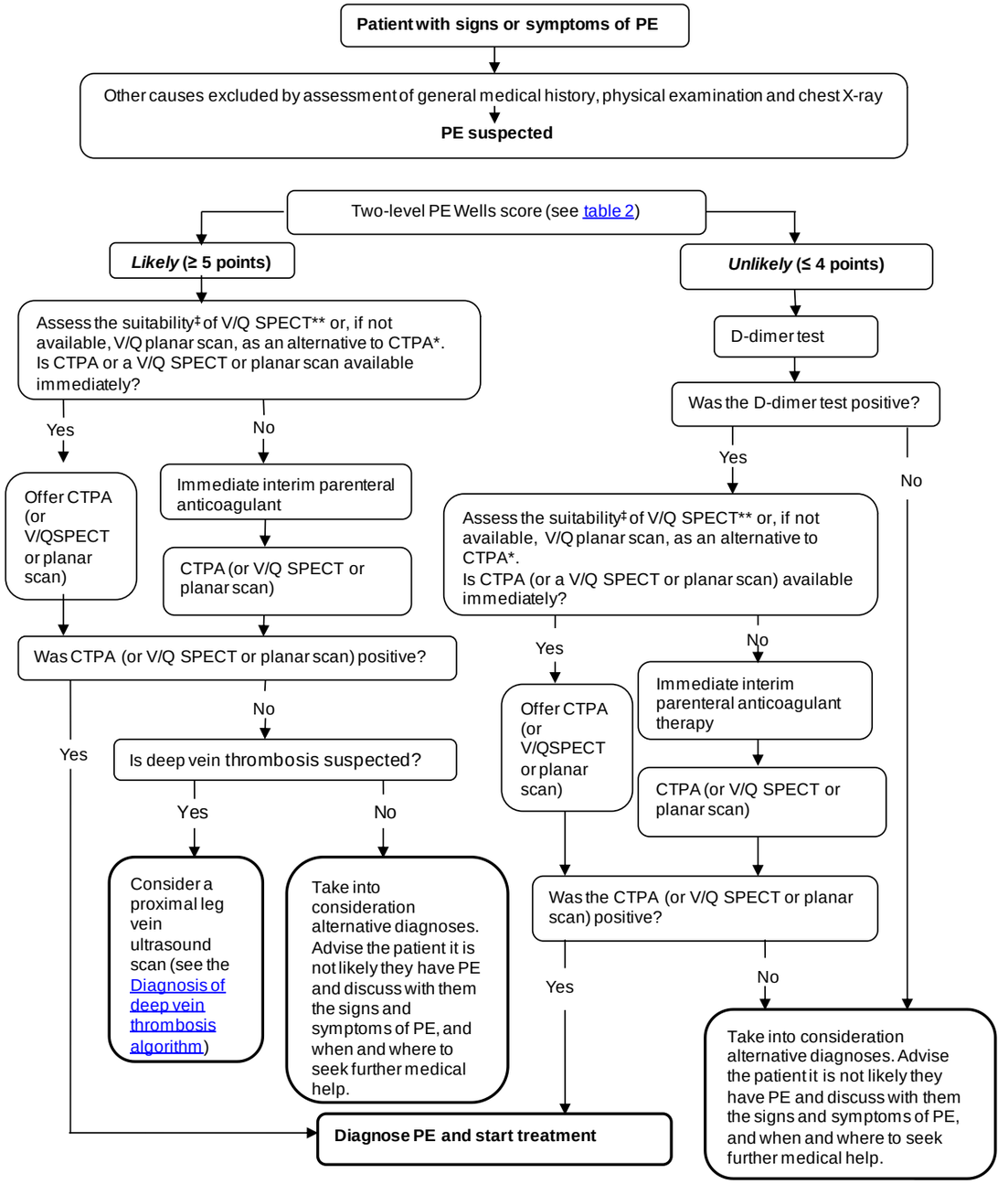
Recommendations	**13. Take into consideration alternative diagnoses in the following two groups of patients:** • **Patients with an *unlikely* two-level PE Wells score and *either*** - **a negative D-dimer test *or*** - **a positive D-dimer test and a negative CTPA.** • **Patients with a *likely* two-level PE Wells score and *both*** - **a negative CTPA *and*** - **no suspected DVT.** **Advise these patients that it is not likely they have PE and discuss with them the signs and symptoms of PE, and when and where to seek further medical help.**
Relative values of different outcomes	The numbers of PE missed (false negatives) is the most important outcome for diagnostic strategies of PE. For this recommendation, the most important issues are ensuring alternative diagnoses are considered, patients are aware of signs and symptoms of PE and knowing when to seek further help if necessary.
Trade off between clinical benefits and harms	Among the groups of patients identified in the recommendation, there is a very low risk of PE and it is not beneficial to subject patients to further tests. The potential harms for more testing (exposing patients to more radiations and anxiety) or starting patients on treatment are likely to outweigh any benefit from not missing PE in a very small number of patients. It will be beneficial and reassuring for patients to know that they are very unlikely to have a PE. However, they should be fully informed of signs and symptoms and when to seek help if new signs and symptoms appear or recur.
Economic considerations	Ruling out PE in people with an “unlikely” PE Wells score and a negative D-dimer was part of the most cost-effective strategy in the economic model developed. For this group of people an alternative diagnosis should be considered. The cost and QALYs loss by the few false negative cases are outweighed by the savings in further tests or unnecessary treatments.
Quality of evidence	The evidence reviewed suggested that very few people actually have PE if their PE Wells score is “unlikely” and their D-dimer test is negative. The review on CTPA showed that it is a sensitive and specific test, despite potential limitations in the evidence.

Recommendations	**13. Take into consideration alternative diagnoses in the following two groups of patients:** • **Patients with an *unlikely* two-level PE Wells score and *either*** - **a negative D-dimer test *or*** - **a positive D-dimer test and a negative CTPA.** • **Patients with a *likely* two-level PE Wells score and *both*** - **a negative CTPA *and*** - **no suspected DVT.** **Advise these patients that it is not likely they have PE and discuss with them the signs and symptoms of PE, and when and where to seek further medical help.**
	The economic evidence has potentially serious limitations and direct applicability.
Other considerations	The presence of signs and symptoms which suggest a possible DVT should be considered and investigated, before PE is ruled out and patients are sent home. See recommendation 9 about using a proximal leg vein ultrasound scan if CTPA is negative in this group.

Recommendations	**14. If a patient presents with signs or symptoms of both DVT (for example a swollen and/or painful leg) and PE (for example chest pain, shortness of breath or haemoptysis), carry out initial diagnostic investigations for either DVT or PE, basing the choice of diagnostic investigations on clinical judgement.**
Relative values of different outcomes	The most important outcome is to follow the appropriate diagnostic pathway, so that the correct treatment can be initiated. It is also important not to miss other alternative diagnosis or causes for the symptoms.
Trade off between clinical benefits and harms	Following the correct diagnostic path means diagnosis can be confirmed accurately and appropriate treatment plans initiated and continued. Unnecessary radiation exposure was also considered. Chest CT is approximately equivalent to 3.6 years of natural background radiation (UK average 2.2 mSv per year taken from referral guideline from the Royal College of Radiologists)[208]. It is unlikely that there are harms from following this recommendation.
Economic considerations	Diagnostic pathways for PE and for DVT have different costs. Given the importance of long-term management, the GDG thought it was cost-effective to confirm both diagnoses when required.
Quality of evidence	This is a supporting recommendation and was made based on GDG consensus.
Other considerations	The GDG discussed the advantages and disadvantages to the patient in following each pathway: • The ultrasound scan used in the DVT algorithm avoids radiation exposure and the administration of contrast compared with CTPA which is used in the PE diagnostic algorithm. A CTPA is approximately equivalent to 3.6 years of natural background radiation (UK average 2.2 mSv per year taken from referral guideline from the Royal College of Radiologists).

Recommendations	**14. If a patient presents with signs or symptoms of both DVT (for example a swollen and/or painful leg) and PE (for example chest pain, shortness of breath or haemoptysis), carry out initial diagnostic investigations for either DVT or PE, basing the choice of diagnostic investigations on clinical judgement.**
	• One advantage of CTPA is that it also looks at all of the other structures within the chest including whether there is evidence of right ventricular dilatation which has prognostic implications and can identify other causes for the patient's symptoms. • The DVT diagnosis algorithm may be chosen for a patient with a possible provoked DVT and PE because there will be no change to the pharmacological treatment as a result of diagnosis and they would be exposed to no radiation or intravenous contrast (see recommendations in section 7.5).

Diagnosis of PE algorithm



‡For patients who have an allergy to contrast media, or who have renal impairment, or whose risk from irradiation is high, assess the suitability of a V/Q SPECT or, if V/Q SPECT is not available, a V/Q planar scan, as an alternative to CTPA.

*Computed tomography pulmonary angiogram

**Ventilation/perfusion single photon emission computed tomography

7 Pharmacological interventions

7.1 Introduction

The pharmacological treatment of VTE is reviewed in three sections for this chapter. The first section looks at the pharmacological management of VTE in the initial stages, followed by strategies for continuing anticoagulation. The last section looks at the optimal length of time for anticoagulation.

The same classes of agents and doses are used for the treatment of PE and DVT. Therefore, the treatment of these conditions was reviewed together (see review question 7.1.1 and 7.1.2 below). However, the meta-analysis, where possible, subgroups these populations to investigate whether there are any differences.

7.1.1 What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed DVT?

7.1.2 What is the effectiveness of pharmacological interventions to manage patients with suspected or confirmed PE?

To answer these questions, we searched for RCTs comparing the clinical effectiveness of different pharmacological interventions for VTE. The interventions included in our comparison for initial and continuation treatment were unfractionated heparins (UFH), low molecular weight heparins (LMWH), synthetic pentasaccharides (SP), vitamin K antagonists (VKA) and placebo. We looked for any studies that compared the effectiveness of two or more of these. Matrices showing the number of studies found for each comparison are available in the initial treatment and continuation treatment sections respectively (see 7.2.1 and 7.3.1).

7.2 Pharmacological interventions for the initial phase of treatment

This section looks at the recommendations for the initial period of therapy, from the confirmation of VTE diagnosis until the continuation phase of treatment is established.

It is important that a therapeutic level of anticoagulation is achieved quickly for patients with VTE. At the time of the guideline review UFH, LMWH and SP were the only products with marketing authorisation in the UK for the initial treatment of VTE. There is only one licensed SP; fondaparinux sodium, which will be referred to as fondaparinux in this guideline. All these are injectable products, which achieve anticoagulation rapidly compared to VKAs, which may take days to become effective. UFH and LMWH are naturally occurring porcine derived products which inhibit blood coagulation. They potentiate the inhibition of several activated coagulation factors, including thrombin and factor Xa, by antithrombin. Fondaparinux acts indirectly, via antithrombin, to selectively inhibit activated factor X (Xa).

For each pharmacological option available it is important to consider: clinical safety and effectiveness, patient preference, and costs associated with initiating treatment of VTE (including nursing time and monitoring costs). Other important considerations, which could affect the suitability of administering these products at home, and may have important cost implications are: the practicality of administering these treatments, for example the number of administrations per day, and the therapeutic monitoring required.

Although most products are licensed for both DVT and PE (with the exception of haemodynamically unstable PE), subgroup analysis was conducted to investigate whether these agents are equally safe

and effective for both initial presentations. Where data was available subgroup analysis was also conducted for patients with cancer.

7.2.1 Initial phase of treatment: Matrix of treatment comparisons

Below is a matrix showing where clinical evidence was identified, and the number of studies found for each comparison for initial pharmacological treatment.

Fondaparinux				
LMWH	1			
UFH	1	18		
Placebo	None	None	None	
	Fondaparinux	**LMWH**	**UFH**	**Placebo**

Note: LMWH = low molecular weight heparin, UFH = unfractionated heparin.

7.2.2 Fondaparinux vs LMWH

7.2.2.1 Clinical evidence

See clinical evidence tables in Appendix E.7 and forest plots in Appendix G.3.1.

There was only one RCT comparing fondaparinux with LMWH. It only included patients with acute DVT confirmed by ultrasonography or venography, and excluded patients with symptomatic PE. Patients in the LMWH group received doses which are higher than the UK licensed doses (1.0 mg/kg body weight twice daily [2.0/mg/kg per day] compared to the UK licensed dose of 1.5 mg/kg body weight per day).

Table 35: Fondaparinux vs LMWH - Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
All cause mortality[28]	1	RCT	No serious limitations	No serious inconsistency	Serious indirectness[(a)]	Serious imprecision[(b)]
VTE related mortality[28]	1	RCT	No serious limitations	No serious inconsistency	Serious indirectness[(a)]	Serious imprecision[(b)]
Recurrent VTE rates[28]	1	RCT	No serious limitations	No serious inconsistency	Serious indirectness[(a)]	Serious imprecision[(b)]
Major bleeding[28]	1	RCT	No serious limitations	No serious inconsistency	Serious indirectness[(a)]	Serious imprecision[(b)]
Fatal bleeding[28]	1	RCT	No serious limitations	No serious inconsistency	Serious indirectness[(a)]	Very serious imprecision[(c)]
Intracranial bleeding/haemorrhage	0		-	-	-	-
Quality of Life	0	-	-	-	-	-
PTS	0	-	-	-	-	-

(a) The dose used for the comparator (LMWH) is higher than the UK licensed dose, this may favour fondaparinux for bleeding outcomes and LMWH for efficacy outcomes. In addition, there is no direct comparison between fondaparinux and LMWH for patients who presented with PE.

(b) The 95% CI crosses MID.

(c) Very wide 95% CI crossing both MIDs, the data were very sparse.

Table 36: Fondaparinux vs LMWH - Clinical summary of findings

Outcome	Fondaparinux	LMWH	Relative risk (95%) CI)	Absolute effect	Quality
All cause mortality	41/1098 (3.7%)	33/1107 (3.0%)	1.25 (0.80, 1.97)	7 more per 1000 (6 fewer to 29 more)	LOW
VTE related mortality	5/1098 (0.5%)	5/1107 (0.5%)	1.01 (0.29, 3.47)	0 more per 1000 (3 fewer to 11 more)	LOW
Recurrent VTE	43/1098 (3.9%)	45/1107 (4.1%)	0.96 (0.64, 1.45)	2 fewer per 1000 (15 fewer to 18 more)	LOW
Major bleeding	28/1098 (2.6%)	26/1107 (2.3%)	1.09 (0.64, 1.84)	2 more per 1000 (8 fewer to 20 more)	LOW
Fatal bleeding	5/1098 (0.4%)	0/1107	11.09 (0.61, 200.32)	-	VERY LOW

7.2.2.2 Economic evidence

No economic evaluations comparing fondaparinux with LMWH were identified. We calculated the daily cost of different pharmacological treatments based on the unit cost reported in the BNF 60[111] (see Table 37 below).

Table 37: Daily cost of drug treatment

Item	Daily cost of drug treatment	Notes
UFH	£5.06 (+initial 1.94)	Dosage of 15 000 units every 12 hours (cost of a 5ml amp containing 5000units/ml) + initial one-off dose of 5000 units (cost of a 1ml amp containing 5000units/ml).
Fondaparinux	£11.66	Dosage of 7.5mg once daily, assuming average weight 70kg (cost of a 0.6ml (7.5mg) prefilled syringe.
LMWH		Assuming average weight of 70kg:
Bemiparin	£4.39	Cost of 0.4-mL (10 000-unit) prefilled syringe
Dalteparin	£8.47	Cost of 15 000-unit (0.6-mL) syringe
Enoxaparin	£9.77	Cost of 120-mg (0.8-mL, 12 000-units) syringe
Tinzaparin	£11.85	Cost of 0.7-mL (14 000-unit) syringe

Source: BNF 60[111]

7.2.2.3 Evidence statements

Clinical

One study in 2205 people suggested that there may be an increase in all cause mortality in the fondaparinux group compared to the LMWH group, but it is uncertain whether this difference is clinically important because the event rate was low (LOW QUALITY).

One study in 2205 people showed it is very uncertain whether there is a clinically important difference in VTE related mortality between the fondaparinux group and the LMWH group (LOW QUALITY).

One study in 2205 people showed it is uncertain whether there is a clinically important difference in recurrent VTE rates between the fondaparinux group and the LMWH group (LOW QUALITY).

One study in 2205 people showed it is uncertain whether there is a clinically important difference in the number of people with major bleeding between the fondaparinux group and the LMWH group (LOW QUALITY).

One study in 2205 people suggested that there may be an increase in fatal bleeding in the fondaparinux group compared to the LMWH group, but it is very uncertain whether this difference is clinically important because the event rate was very low (VERY LOW QUALITY).

Economic — No economic evidence was found for this question. A simple cost analysis showed a difference in drug costs between UFH, LMWH and fondaparinux. On average, fondaparinux is the most costly option.

7.2.3 Fondaparinux vs UFH

7.2.3.1 Clinical evidence

See clinical evidence tables in Appendix E.7 and forest plots in Appendix G.3.2.

Only one RCT was included in the evidence review. The population of this study was comprised exclusively of patients with acute symptomatic PE. The included study carried out subgroup analyses on cancer patients.

Table 38: Fondaparinux vs UFH– Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
All cause mortality[29]	1	RCT	Serious limitations[(a, b)]	No serious inconsistency	No serious indirectness[(c)]	Serious imprecision[(d)]
VTE related mortality[29]	1	RCT	Serious limitations[(a, b)]	No serious inconsistency	No serious indirectness[(c)]	Serious imprecision[(d)]
Recurrent VTE rates (all patients)[29]	1	RCT	Serious limitations[(a, b)]	No serious inconsistency	No serious indirectness[(c)]	Serious imprecision[(d)]
Subgroup: Cancer patients[29]	*1*	*RCT*	*Serious limitations[(a, b)]*	*No serious inconsistency*	*No serious indirectness[(c)]*	Serious imprecision[(d)]
Major bleeding (all patients)[29]	1	RCT	Serious limitations[(a, b)]	No serious inconsistency	No serious indirectness[(c)]	Serious imprecision[(d)]
Subgroup: Cancer patients[29]	*1*	*RCT*	*Serious limitations*[(a, b)]	*No serious inconsistency*	*No serious indirectness[(c)]*	*Serious imprecision[(d)]*
Fatal bleeding (all patients)[29]	1	RCT	Serious limitations[(a, b)]	No serious inconsistency	No serious indirectness[(c)]	Very serious imprecision[(e)]
Intracranial bleeding/ haemorrhage	0	-	-	-	-	-
Quality of Life	0	-	-	-	-	-

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
PTS	0	-	-	-	-	-

(a) Allocation concealment unclear.
(b) Randomisation unclear.
(c) The study only included people with acute symptomatic PE, and therefore there is no direct comparison between fondaparinux and UFH for patients with DVT. However, there is no further downgrading because most of these patients are also likely to have DVT.
(d) The 95% CI crosses MID.
(e) The 95% CI crosses both MID, the data were very sparse.

Table 39: Fondaparinux vs UFH– Clinical summary of findings

Outcome	Fondaparinux	UFH	Relative risk	Absolute effect	Quality
All cause mortality	57/1103 (5.2%)	48/1110 (4.3%)	1.2 (0.82, 1.74)	9 more per 1000 (8 fewer to 32 more)	LOW
VTE related mortality	16/1103 (1.5%)	15/1110 (1.4%)	1.07 (0.53, 2.16)	1 more per 1000 (6 fewer to 16 more)	LOW
Recurrent VTE rates (all patients)	42/1103 (3.8%)	56/1110 (5.1%)	0.75 (0.51, 1.12)	13 fewer per 1000 (25 fewer to 6 more)	LOW
Subgroup: Cancer patients	*10/112 (8.9%)*	*22/128 (17.2%)*	*0.52 (0.26, 1.05)*	*83 fewer per 1000 (127 fewer to 9 more)*	*LOW*
Major bleeding (all patients)	22/1103 (2%)	26/1110 (2.3%)	0.85 (0.49, 1.49)	4 fewer per 1000 (12 fewer to 11 more)	LOW
Subgroup: Cancer patients	*2/112 (1.8%)*	*3/128 (2.3%)*	*0.76 (0.13, 4.48)*	*6 fewer per 1000 (20 fewer to 82 more)*	*LOW*
Fatal bleeding	3/1103 (0.3%)	1/1110 (0.1%)	3.02 (0.31, 28.98)	2 more per 1000 (1 fewer to 25 more)	VERY LOW

7.2.3.2 Economic evidence

No economic evaluations comparing fondaparinux with UFH were identified. We calculated the daily cost of different pharmacological treatments based on the unit cost reported in the BNF 60[111] (see Table 37 in section 7.2.2.2).

7.2.3.3 Evidence statements

Clinical

One study in 2213 people suggested that there may be an increase in all cause mortality in the fondaparinux group compared to the UFH group, but it is uncertain whether this difference is clinically important because of the event rate was low (LOW QUALITY).

One study in 2213 people showed it is uncertain whether there is a clinically important difference in VTE related mortality between the fondaparinux group and the UFH group (LOW QUALITY).

One study in 2213 people showed there was a decrease which may be of clinical importance in the fondaparinux group compared to the UFH group for recurrent VTE rates (LOW QUALITY).

In the cancer subgroup: one study in 240 people showed there was a decrease which may be of clinical importance in the fondaparinux group compared to the UFH group for recurrent VTE rates (LOW QUALITY).

One study in 2213 people showed it is uncertain whether there is a clinically important in major bleeding between the fondaparinux group and the UFH group (LOW QUALITY).

In the cancer subgroup: one study in 240 people showed it is very uncertain whether there is a clinically important difference in major bleeding between the fondaparinux group and the UFH group (LOW QUALITY).

One study in 2213 people suggested that there may be an increase in fatal bleeding in the fondaparinux group compared to the LMWH group, but it is very uncertain whether this difference is clinically important because the event rate was very low (VERY LOW QUALITY).

Economic — No economic evidence was found for this question. A simple cost analysis showed a difference in drug costs between UFH, LMWH and fondaparinux. Fondaparinux is on average the most costly option.

7.2.4 LMWH vs UFH

7.2.4.1 Clinical evidence

Eighteen studies comparing LMWH and UFH were found and included.

See clinical evidence tables in Appendix E.7 and forest plots in Appendix G.3.3.

Table 40: LMWH vs UFH – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
All cause mortality (at 3 months) – all patients[48,68,69,102,103,116,119,131,140,149,151,160,161,175,195,196,227,228]	18	RCT	Serious limitations[(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]
Subgroup: Acute PE[69,102,161,228]	*4*	*RCT*	*Serious limitations*[(a)]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision* [(b)]
Subgroup: DVT or PE[48,103,119,151,160,175,195,227]	*8*	*RCT*	*Serious limitations*[(a)]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision* [(b)]
Subgroup: DVT only (symptomatic PE excluded)[68,116,131,140,149,196]	*6*	*RCT*	*Serious limitations*[(a)]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision* [(b)]
VTE related mortality (at 3 months)[34,69,102,103,119,131,140,144,151,160,161,175,195,196,227,228]	16	RCT	Serious limitations[(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]
Subgroup: Acute PE[69,102,161,228]	*4*	*RCT*	*Serious limitations*[(a)]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision* [(b)]
Subgroup: DVT or PE[103,119,151,160,175,195,227]	*7*	*RCT*	*Serious limitations*[(a)]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision* [(b)]
Subgroup: DVT only (symptomatic PE excluded)[34,131,140,144,196]	*5*	*RCT*	*Serious limitations*[(a)]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision* [(b)]
Recurrent VTE (at 3 months)[27,48,69,102,103,116,119,131,140,149,160,161,175,195,196,200,227,228]	18	RCT	Serious limitations[(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]
Major bleeding (at 3 months)[48,69,102,116,119,131,149,195,196,228]	11	RCT	Serious limitations[(a),(c)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]
Fatal bleeding (at 3 months)[34,102,103,116,119,131,149,160,161,175,195,196,227,228]	14	RCT	Serious limitations[(a),(c),(d)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]
Intracranial bleeding (at 3 months)[34,102,103,116,119,131,149,196,200,227,228]	11	RCT	Very serious limitations[(a),(c),(d)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]
PTS[27]	1	RCT	Very serious limitations[(a),(d), (e)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]
Heparin induced	7	RCT	Very serious	No serious	No serious	Serious

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
thrombocytopenia[34, 102,103,119,195,200,228]			limitations[(a), (d)]	inconsistency	indirectness	imprecision [(b)]
Quality of life[131]	1	RCT	Very serious limitations[(a), (d)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b)]
Chronic thromboembolic pulmonary hypertension	0	RCT	-	-	-	-

(a) 18 studies had unclear methods of randomisation and allocation concealment. The majority of studies were not blinded, and most studies allowed exposure to UFH before randomisations, for usually up to 24 hours. 1 study was a 2x2 factorial design, randomising patients to vena caval filter or no filter, and LMWH vs UFH. [48] Some patients were unaccounted for in some studies. However, sensitivity analysis with available cases analysis did not show any important difference in results (no further downgrading).

(b) The CIs crossed one or more MID thresholds.

(c) The definition of bleeding was unclear in some studies.

(d) Not all studies reported these outcomes. It was unclear whether these outcomes were always reported.

(e) It was unclear whether the questionnaire was valid and reliable for PTS.

Table 41: LMWH vs UFH: Clinical summary of findings

Outcome	LMWH	UFH	Relative risk	Absolute effect	Quality
All cause mortality (at 3 months) – all patients	115/3226 (3.6%)	139/2949 (4.7%)	RR 0.78 (0.61 to 0.99)	10 fewer per 1000 (from 0 fewer to 18 fewer)	LOW
Subgroup: Acute PE	*19/459 (4.1%)*	*24/472 (5.1%)*	*RR 0.82 (0.45 to 1.47)*	*9 fewer per 1000 (from 28 fewer to 24 more)*	*LOW*
Subgroup: DVT or PE	*73/1903 (3.8%)*	*75/1605 (4.7%)*	*RR 0.86 (0.63 to 1.19)*	*7 fewer per 1000 (from 17 fewer to 9 more)*	*LOW*
Subgroup: DVT only (symptomatic PE excluded)	*23/864 (2.7%)*	*40/872 (4.6%)*	*RR 0.59 (0.36 to 0.97)*	*19 fewer per 1000 (from 1 fewer to 29 fewer)*	*LOW*
VTE related mortality (at 3 months)	16/2952 (0.54%)	18/2659 (0.68%)	RR 0.82 (0.44 to 1.55)	1 fewer per 1000 (from 4 fewer to 4 more)	LOW
Subgroup: Acute PE	*3/459 (0.65%)*	*4/472 (0.85%)*	*RR 0.8 (0.2 to 3.21)*	*2 fewer per 1000 (from 7 fewer to 19 more)*	*LOW*
Subgroup: DVT or PE	*11/1708 (0.64%)*	*9/1400 (0.64%)*	*RR 1.01 (0.45 to 2.29)*	*0 more per 1000 (from 4 fewer to 8 more)*	*LOW*
Subgroup: DVT only (symptomatic PE excluded)	*2/785 (0.25%)*	*5/787 (0.64%)*	*RR 0.46 (0.1 to 2.02)*	*3 fewer per 1000 (from 6 fewer to 6 more)*	*LOW*
Recurrent VTE (at 3 months)	104/3127 (3.3%)	128/2822 (4.3%)	RR 0.77 (0.6 to 1)	10 fewer per 1000 (from 17 fewer to 0 more)	LOW
Major bleeding (at 3 months)	45/1941 (2.3%)	64/1958 (3.3%)	RR 0.72 (0.5 to 1.04)	9 fewer per 1000 (from 16 fewer to 1 more)	LOW
Fatal bleeding (at 3 months)	7/2658 (0.3%)	10/2340 (0.4%)	RR 0.55 (0.21 to 1.41)	2 fewer per 1000 (from 3 fewer to 2 more)	LOW
Intracranial bleeding (at 3 months)	1/1775 (0.1%)	5/1675 (0.3%)	RR 0.46 (0.14 to 1.5)	2 fewer per 1000 (from 3 fewer to 1 more)	VERY LOW
PTS	N=41	N=43	-	MD 2.45 lower (6.16 lower to 1.26 higher)	VERY LOW
Heparin induced thrombocytopenia	6/1124 (0.5%)	5/1127 (0.4%)	RR 1.19 (0.4 to 3.49)	1 more per 1000 (from 3 fewer to 11 more)	VERY LOW
Quality of life	N=70	-	-	No statistically significant difference, except for social and physical functioning while on therapy (1-2 weeks).	VERY LOW

7.2.4.2 Economic evidence

Five studies were reviewed that included the relevant comparison.[11,31,82,86,247] These are summarised in the economic evidence profile below (Table 42 and Table 43). See also the full study evidence tables in Appendix F.

Other studies were found that could have been potentially included but were eventually excluded because better evidence was available. The excluded studies are summarised in Table 42 below.

Table 42 - Excluded economic studies

First author	Title	Journal	Publication year	Reason for exclusion
Avritscher[13]	Cost-minimization analysis of low molecular weight heparin (dalteparin) compared to unfractionated heparin for inpatient treatment of cancer patients with deep venous thrombosis.	*Supportive Care in Cancer*	2004	Cost analysis from the USA (better evidence available)
Daskalopoulos[45]	Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial.	*European Journal of Vascular and Endovascular Surgery*	2005	Only unit cost of drugs, from Greece (better evidence available)
De Lissovoy[47]	Cost for inpatient care of venous thrombosis: a trial of enoxaparin vs standard heparin.	*Archives of Internal Medicine*	2000	Cost analysis from the USA (better evidence available)
Estrada[65]	Cost-effectiveness of low-molecular-weight heparin in the treatment of proximal DVT.	*Journal of General Internal Medicine*	2000	Cost-effectiveness analysis (QALYs not evaluated) from the USA (better evidence available).
Heaton[91]	Low molecular weight versus unfractioned herapin: a clinical and economic appraisal.	*PharmacoEconomics*	1995	Cost analysis from New Zealand (better evidence available)
Hull[104]	Treatment of proximal vein thrombosis with subcutaneous low molecular weight heparin vs intravenous heparin: an economic perspective.	*Archives of Internal Medicine*	1997	Cost-consequences analysis (QALYs not evaluated) from Canada (better evidence available).
Hull[100]	The economic impact of treating DVT with low-molecular-weight heparin: outcome of therapy and health economy aspects.	*Haemostasis*	1998	Cost analysis from Canada (better evidence available)
Kremenski[133]	Pharmacoeconomic assessment of deep venous thrombosis.	*Farmaceutski Glasnik*	2001	Cost analysis from Bulgaria (better evidence available)
Lloyd[146]	Economic evaluation of the use nadroparin in the treatment of deep-vein thrombosis in Switzerland.	*Annals of Pharmacotherapy*	1997	Cost analysis from Switzerland (better evidence available)
Shorr[224]	Minimizing costs for treating DVT: the role for fondaparinux.	*Journal of Thrombosis and Thrombolysis*	2007	Cost analysis from the USA (better evidence available)

Table 43: LMWH vs UFH – Economic study characteristics

Study	Limitations	Applicability	Other comments
Aujesky 2005[11]	Potentially serious limitations [(a)]	Partial applicability [(b)]	LMWH was enoxaparin for 6 days in a fixed dosage of 1mg/kg subcutaneously bid + warfarin for 3 months. UFH at 30,000 U/d for six days + warfarin for 3 months. Population: patients with acute submassive PE.
Caro 2002[31]	Potentially serious limitations [(c)]	Partial applicability [(d)]	LMWH was tinzaparin sodium, 175 Internation Factor Xa inhibitory units/kg, subcutaneously once daily for 6 days + warfarin for 3 months. UFH for an average of 6 days + warfarin for 3 months. Population: patients with proximal DVT.
Gomez-Outes 2006[82]	Potentially serious limitations [(e)]	Partial applicability [(f)]	LMWH was subcutaneous bemiparin 115 IU/kg/day for 7–10 days + oral anticoagulants. Dose-adjusted UFH for 7 days + oral anticoagulants for three months. Population: patients with proximal DVT.
Gould 1999[86]	Potentially serious limitations [(g)]	Partial applicability [(h)]	LMWH was fixed-dose enoxaparin, 1 mg/kg of body weight subcutaneously, twice daily for 6 days + oral anticoagulants for 3 months. UFH IV at an average dosage of 30 000 U/d for a total of 6 days + oral anticoagulants for 3 months. Population: patients with proximal DVT.
Valette 1995[247]	Potentially serious limitations [(i)]	Partial applicability [(j)]	LMWH was one subcutaneous injection per day of tinzaparin 175 anti-Factor Xa per kg body weight for six days + warfarin for 3 months. UFH 5000 IV bolus dose for six days with intravenous infusion of an average daily dose of 32,000 IV. Nine activated partial thromboplastin time tests to monitor the effect of heparin and two cannulations required over 6 days. Population: patients with DVT.

(a) No sensitivity analysis was conducted on utility values. Late complications were assumed to be equal in the two interventions. Post-thrombotic syndrome was not included.

(b) Societal perspective was adopted (patient time included). Study from the USA. HRQoL values were based on number of days of hospitalisation.

(c) No multi-way sensitivity analysis was performed on event rates of LMWH and UFH. No PSA was conducted. No utility values were attached to the model health states (no disutilities due to events in the model). Long-term cost of stroke was not included.

(d) Study from the USA.

(e) No utility values were attached to the model health states (no disutilities due to events in the model). Costs were calculated only for the first three months. Long-term cost of stroke was not included. Post-thrombotic syndrome was not included. No PSA was conducted. Potential conflict of interests.

(f) Study from Spain.

(g) Incidence of post-phlebitic syndrome and long-term survival were assumed to be the same in the two interventions and were obtained from observational studies. Probabilities of long-term recurrence of DVT and PE used in the model were not reported. No PSA was conducted.

(h) Study from the USA. HRQoL values were based on number of days of hospitalisation.

(i) HIT was not included in the analysis as data from the RCT were not available. Length of follow-up was short and not explicitly reported (assumed three months as in the original RCT). No PSA was conducted. Potential conflict of interests.

(j) Quality of life was not included in the analysis.

Table 44: LMWH versus UFH – Economic summary of findings

Study	Incremental cost per patient (£)	Incremental effects (QALYs) per patient	ICER (£/QALY)	Uncertainty
Aujesky 2005[11]	Saves 138 [(a)]	0.184 [(b)]	LMWH dominant	Scenario analysis where different proportions of patients receiving LMWH were discharged early or treated as outpatients. LMWH was cost saving when at least 8% of patients were discharged early or if at least 5% of patients were treated entirely as outpatients. One-way SA: ICER was always <£2,000/QALY when the following variables were varied: daily cost of LMWH, cost of supplies of UFH, cost of non cerebral MB, annual cost of care after stroke, risk of MB with UFH and LMWH, risk of recurrent PE with LMWH and UFH, early mortality risk with LMWH and UFH, early DVT risk with LMWH and UFH, annual late risk of recurrent PE and DVT, frequency of haemorrhagic stroke. PSA: the median ICER of 1,000 iterations was £751/QALY. At a willingness to pay of $50,000/QALY (about £30,000), LMWH was cost-effective in 99% of the iterations.
Caro 2002[31]	Saves 406 [(c)]	0.53 [(d)]	LMWH dominant	Scenario analysis: if LMWH as outpatient treatment or inpatient treatment with early discharge would be even more cost-saving. One-way SA: results were not sensitive to these parameters: cost of LMWH (when increased by $20), DVT management costs, event rates with LMWH, discount rate.
Gomez-outes 2006[82]	Saves 658 [(e)]	1.72 [(f)]	LMWH dominant	LMWH was still dominant if the initial treatment was followed by long-term bemiparin 3500 IU. One-way SA: LMWH was always cost-saving.
Gould 1999[86]	99 [(g)]	0.02 [(h)]	4,950	Scenario analysis: assuming 30% of patients in LMWH are treated as outpatients and 25% are discharged early after 3 days, LMWH is dominant. Threshold analysis: LMWH is dominant if at least 8% patients are treated as outpatients or at least 13% are discharged after 3 days. One-way SA: results were sensitive to the

Study	Incremental cost per patient (£)	Incremental effects (QALYs) per patient	ICER (£/QALY)	Uncertainty
				assumption that late complications are equal in the two interventions: when late complications are assumed to occur 25% less frequently with UFH, LMWH is not cost-effective. Results were not sensitive to other variables: risk reduction for early complications, death, PE, recurrent DVT, major and minor bleeding, thrombocytopenia, pharmacy costs, cost of complications, utilities for late complications, discount rate. Three-way SA: when pharmacy cost of LMWH, treatment cost of early complications, and effectiveness of LMWH in preventing early complications are varied, LMWH is still cost-effective.
Valette 1995[247]	Saves 52 (i)	NA (j)	NA	Adjusted model: when it was assumed that bleeding events taking place after the end of the therapy are not treatment-related and deaths from causes other than PE or haemorrhage are excluded from the analysis, LMWH saves £64 compared to UFH. LMWH is still cost-saving when the following assumptions were changed: efficacy in prevention of further VTE, frequency of bleeding complications, frequency of APTT tests with UFH, use of clotting factors concentrates instead of fresh frozen plasma.

(a) Cost of drugs, supplies, PE treatment, clinical visits, complications (HIT, minor bleeding, noncerebral major bleeding, acute haemorrhagic stroke, long-term care of stroke, DVT). 2002 USD converted into GBP using the purchasing power parities.

(b) Calculated using days lost because of hospitalisation or disease as proxies of utilities and age-adjusted mean utility values for patients without complications. No difference in utilities between patients treated at home or in hospital.

(c) Cost of initial treatment (including inpatient and outpatient care), major and minor bleeding, recurrent DVT, PE, thrombocytopenia, minor and severe postphlebitic syndrome, recurrent VTE. 1999 USD converted into GBP using the purchasing power parities.

(d) Long term utilities calculated using age-related utilities for general population and utility adjustments for mild and severe postphlebitic syndrome.

(e) Cost of hospital stay, physician, pharmacy costs and costs derived from diagnostic and treatment of complications (minor and major bleeding, thrombocytopenia). 2002 Euro converted into GBP using the purchasing power parities.

(f) Calculated using only age- and gender-adjusted mean utility values for general population; no utilities were attached to events.

(g) Cost of hospital care, physician services, 6 days of treatment, supplies and ancillary resources (needles and daily phlebotomy) for LMWH, complications (1 hospital day+1physician visit for minor bleeding or for thrombocytopenia, 2.5 hospital days+2.5 physician visit for major bleeding; average Medicare reimbursements for others). 1997 USD converted into GBP using the purchasing power parities.

(h) Calculated using age- and gender-adjusted time trade-off utilities for general population in case of no complications. Utilities for postphlebitic syndrome from standard gamble of healthy individuals. Days of hospitalisation were used as a proxy of disutilities for early complications and recurrent DVT and PE.

(i) Cost of initial treatment, repeated treatment in case or recurrence, minor and major bleeding.

(j) Outcomes reported in the trial were recurrence of DVT, PE events, minor bleeding short term and long term, major bleeding short term and long term, death. They were all in favour of LMWH except for minor bleeding short-term and major bleeding long term.

In four[11,31,82,247] of the studies included in the review, LMWH was cost saving compared to UFH; one of these studies[11] was in patients with acute submassive PE while the population in the other studies was patients with DVT. In one study[86] LMWH was more effective but slightly more costly than UFH; however when the assumptions on the treatment setting and the length of stay were changed (at least 8% patients treated as outpatients or at least 13% discharged after 3 days) LMWH became dominant.

7.2.4.3 Evidence statements

Clinical

18 studies in 6175 people showed there was a decrease of uncertain clinical importance in the LMWH group compared to the UFH group for all cause mortality (at 3 months) (LOW QUALITY).

16 studies in 5611 people showed it is uncertain whether there is a clinically important difference in VTE related mortality at 3 months between the LMWH group and UFH group (LOW QUALITY).

18 studies in 5949 people showed there was a decrease of uncertain clinical importance in the LMWH group compared to the UFH group for recurrent VTE (at 3 months) (LOW QUALITY).

11 studies in 3899 people showed there may be a reduction in major bleeding at 3 months between the LMWH and UFH groups but there is uncertainty and the reduction may not be clinically important (LOW QUALITY).

14 studies in 4998 people showed that it is uncertain whether there is a clinically important difference in fatal bleeding at 3 months between the LMWH group and UFH group (LOW QUALITY).

11 studies in 3450 people showed it is uncertain whether there is a clinically important difference in intracranial bleeding at 3 months between the LMWH group and UFH group (VERY LOW QUALITY).

One study in 84 people showed it is uncertain whether there is a clinically important difference in PTS between the LMWH group and UFH group (VERY LOW QUALITY).

Seven studies in 2251 people showed it is very uncertain whether there is a clinically important difference in heparin induced thrombocytopenia between the LMWH group and UFH group (VERY LOW QUALITY).

Quality of life was reported in one study[131] and presented graphically only. P values were included and no differences were seen in baseline. The Medical Outcomes Study Short-Form General Health survey (MOS SF20) showed a statistically significant difference in the “physical exercise” ($p=0.002$) and “social functioning” ($p<0.001$) domains during initial treatment (week 1-2) for LMWH. There was no statistically significant difference in other domains or time points (12 and 24 weeks). The study also used an adaptation of the Rotterdam symptom check list adding four items specific to thrombosis of the leg: swelling, a heavy feeling, pain in the calf and pain in the thigh. No statistically significant difference was found between the LMWH and UFH groups.

	No studies reported chronic thromboembolic pulmonary hypertension as an outcome.
Economic	LMWH is more cost-effective or cost-saving compared to UFH as a short-term treatment for PE or DVT. This evidence has potentially serious limitations and partial applicability.

See recommendations and link to evidence in section 5.5.

7.3 Pharmacological interventions for the continuation phase of treatment

Following the initial diagnosis of VTE a clinical decision is required whether the benefit of anticoagulation outweighs potential risks, such as bleeding. However, in most cases some form of anticoagulation will be required. The length of time anticoagulation is required for is considered in the next section of this chapter (Section 7.4).

For most patients the continuation phase of anticoagulation treatment of VTE is with VKA. Use of drugs such as warfarin has long been established and there are a large number of services within the NHS to ensure that patients can be treated appropriately. More recently, alternatives have become available for the continuation phase of treatment of VTE. LMWH, once the preserve of secondary care, is increasingly used in the community, particularly in people with VTE and active cancer. Oral factor Xa antagonists and oral thrombin antagonists may be a viable alternative to oral VKA. However, at the time the evidence review was conducted, these were not licensed in the UK for the treatment of VTE during the development of the guideline and therefore not considered in this review.

The choice of which drug to use is determined by the type and underlying cause of VTE, patient preference, potential for compliance, and cost. Patients need to be appropriately educated regarding their medication and its potential adverse effects and drug interactions.

For the purpose of this review, only the classes of drugs which had a marketing authorisation for the continuation phase of treatment of VTE were considered.

7.3.1 Matrix of treatment comparisons

Below is a matrix showing where clinical evidence was identified, and the number of studies found for each comparison.

LMWH			
UFH	None		
VKA	16	None	
Placebo	None	None	None
	LMWH	**UFH**	**VKA**

7.3.2 LMWH vs VKA

7.3.2.1 Clinical evidence

See clinical evidence tables in Appendix E.7 and forest plots in Appendix G.3.4.

Table 45: LMWH vs VKA – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
All cause mortality -all patients[21,32,44,45,49,83,90,99,138,148,150,162,185,194,207,253]	16	RCT	Serious limitations[a]	No serious inconsistency	No serious indirectness	No serious imprecision
Subgroup: DVT[32,44,45,83,90,99,148,150,194,207,253]	*11*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[b]
Subgroup: PE[21,185]	*2*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[b]
Subgroup: DVT or PE[49,138,162]	*3*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[b]
Subgroup: Non cancer[21,44,45,83,90,148,150,185,194,207,253]	*11*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[b]
Subgroup: Cancer patients[32,49,99,138,150,162,207]	*7*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*No serious imprecision*
VTE related mortality[21,45,83,185,207]	5	RCT	Serious limitations[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]
Subgroup: DVT[45,83,207]	*3*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[b]
Subgroup: PE[21,185]	*2*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[b]
Recurrent VTE rates - all patients[21,44,45,49,83,84,90,99,138,148,150,162,185,194,207,253]	16	RCT	Serious limitations[a]	Serious inconsistency	No serious indirectness	No serious imprecision
Subgroup: DVT[44,45,83,84,90,99,148,150,194,207,253]	*11*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[b]
Subgroup: PE[21,185]	*2*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[b]
Subgroup: DVT or PE[49,138,162]	*3*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*No serious imprecision*
Subgroup: Non cancer[21,44,45,83,84,90,148,150,185,194,207,253]	*12*	*RCT*	*Serious limitations*[a]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[b]

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Subgroup: Cancer patients[49,99,138,150,162]	*5*	*RCT*	*Serious limitations* [(a)]	*No serious inconsistency*	*No serious indirectness*	*No serious imprecision*
Major bleeding - all patients[21,44,45,49,83,90,99,138,148,150,162,185,194,207,253]	15	RCT	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision[(b)]
Subgroup: Non cancer[21,44,45,83,90,148,150,185,194,207,253]	*11*	*RCT*	*Serious limitations* [(a)]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[(b)]
Subgroup: Cancer patients[49,99,138,150,162]	*5*	*RCT*	*Serious limitations* [(a)]	*No serious inconsistency*	*No serious indirectness*	*Serious imprecision*[(b)]
Fatal bleeding[45,185,207]	3	RCT	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b, c)]
Intracranial bleed/haemorrhage[185]	1	RCT	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b, c)]
PTS[84]	1	RCT	Serious limitations [(a)]	No serious inconsistency	No serious indirectness	Serious imprecision [(b, c)]
Quality of life	0	RCT	-	-	-	-

(a) Most studies had unclear randomisation methods and allocation concealment, all were open label studies.
(b) The CIs were wide and crossed MIDs.
(c) Not all studies consistently reported these outcomes; there is a possibility of reporting bias.

Table 46: LMWH vs VKA – Clinical summary of findings

Outcome	LMWH	VKA	Relative risk	Absolute effect	Quality
All cause mortality - all patients	247/1499 (16.5%)	239/1454 (16.4%)	RR 0.99 (0.85 to 1.15)	2 fewer per 1000 (from 25 fewer to 25 more)	MODERATE
Subgroup: DVT	*69/933 (7.4%)*	*63/939 (6.7%)*	*RR 1.1 (0.79 to 1.51)*	*7 more per 1000 (from 14 fewer to 34 more)*	*LOW*
Subgroup: PE	*4/92 (4.3%)*	*0/70*	*RR 3.28 (0.38 to 28.33)*	*Not estimable*	*LOW*
Subgroup: DVT or PE	*174/474 (36.7%)*	*176/445 (39.6%)*	*RR 0.94 (0.79 to 1.11)*	*24 fewer per 1000 (from 83 fewer to 44 more)*	*LOW*
Subgroup: Non cancer	*42/776 (5.4%)*	*33/762 (4.3%)*	*RR 1.23 (0.8 to 1.9)*	*10 more per 1000 (from 9 fewer to 39 more)*	*LOW*
Subgroup: Cancer patients	*205/723 (28.4%)*	*206/692 (29.8%)*	*RR 0.95 (0.81 to 1.11)*	*15 fewer per 1000 (from 57 fewer to*	*MODERATE*

Outcome	LMWH	VKA	Relative risk	Absolute effect	Quality
				33 more)	
VTE related mortality	4/354 (1.1%)	2/335 (0.6%)	RR 1.35 (0.31 to 5.92)	2 more per 1000 (from 4 fewer to 29 more)	LOW
Subgroup: DVT	*2/262 (0.76%)*	*2/265 (0.75%)*	*RR 1.02 (0.18 to 5.84)*	*0 more per 1000 (from 6 fewer to 37 more)*	*LOW*
Subgroup: PE	*2/92 (2.2%)*	*0/70*	*R 2.56 (0.13 to 50.95)*	*Not estimable*	*LOW*
Recurrent VTE rates - all patients	116/1482 (7.8%)	166/1434 (11.6%)	RR 0.68 (0.54 to 0.85)	37 fewer per 1000 (from 17 fewer to 53 fewer)	MODERATE
Subgroup: DVT	*79/922 (8.6%)*	*107/923 (11.6%)*	*RR 0.74 (0.56 to 0.97)*	*30 fewer per 1000 (from 3 fewer to 51 fewer)*	*LOW*
Subgroup: PE	*4/92 (4.3%)*	*0/70*	*RR 3.28 (0.38 to 28.33)*	*Not estimable*	*VERY LOW*
Subgroup: DVT or PE	*33/468 (7.1%)*	*59/441 (13.4%)*	*RR 0.53 (0.35 to 0.79)*	*63 fewer per 1000 (from 28 fewer to 87 fewer)*	MODERATE
Subgroup: Non cancer	*75/897 (8.4%)*	*87/875 (9.9%)*	*RR 0.85 (0.63 to 1.13)*	*15 fewer per 1000 (from 37 fewer to 13 more)*	*LOW*
Subgroup: Cancer patients	*41/585 (7%)*	*79/559 (14.1%)*	*RR 0.5 (0.35 to 0.71)*	*71 fewer per 1000 (from 41 fewer to 92 fewer)*	*MODERATE*
Major bleeding - all patients	47/1405 (3.3%)	56/1357 (4.1%)	RR 0.79 (0.55 to 1.16)	9 fewer per 1000 (from 19 fewer to 7 more)	LOW
Subgroup: Non cancer	*10/812 (1.2%)*	*21/795 (2.6%)*	*RR 0.48 (0.24 to 0.97)*	*14 fewer per 1000 (from 1 fewer to 20 fewer)*	*LOW*
Subgroup: Cancer patients	*37/593 (6.2%)*	*35/562 (6.2%)*	*RR 1 (0.64 to 1.58)*	*0 fewer per 1000 (from 22 fewer to 36 more)*	*LOW*
Fatal bleeding	1/221 (0.45%)	1/224 (0.45%)	RR 1.04 (0.07 to 16.18)	0 more per 1000 (from 4 fewer to 68 more)	VERY LOW
Intracranial bleed/haemorrhage	0/52	0/50	-	not pooled	VERY LOW
PTS	34/85 (40%)	31/80 (38.8%)	RR 1.03 (0.71 to 1.51)	12 more per 1000 (from 112 fewer to 198 more)	VERY LOW
Quality of life	-	-	-	-	-

7.3.2.2 Economic evidence

Four studies were included that compared LMWH with VKA[10,59,154,185]. These are summarised in the economic evidence profile below (Table 47 and Table 48). See also the full study evidence tables in Appendix F.

No relevant economic evaluations including other treatments (i.e. UFH, placebo or fondaparinux) were identified and a simple cost analysis was performed (see Table 37 in section 7.2.2.2).

Table 47: LMWH vs VKA – Economic study characteristics

Study	Limitations	Applicability	Other comments
Aujesky 2005[10]	Potentially serious limitations [(a)]	Partially applicable [(b)]	Cancer patients. Decision analysis with lifetime extrapolation based on Lee 2003[138]. LMWH was dalteparin for 6 months and VKA was warfarin for 6 months (first 5 days with LMWH too).
Dranitsaris 2006[59]	Potentially serious limitations [(c)]	Partially applicable [(d)]	Cancer patients. Decision analysis based on Lee 2003[138], with the same time horizon (6 months). LMWH was dalteparin for 6 months and VKA was first 7 days with dalteparin followed by warfarin for 6 months.
Marchetti 2001[154]	Potentially serious limitations [(e)]	Partially applicable [(f)]	DVT patients, 15% with cancer. LMWH was enoxaparin for 3 months with a 95% compliance and VKA was first 5 days with LMWH followed by warfarin for 3 months.
Perez-de-llano 2010[185]	Potentially serious limitations [(g)]	Partially applicable [(h)]	PE patients. RCT included in meta-analysis. LMWH was tinzaparin for 6 months and VKA was acenocumarol.

(a) In this RCT the incidence of major bleeding was higher in the LMWH group but the overall results of our meta-analysis show the opposite. Cost of stroke was not included in the analysis.

(b) Cost of home nursing might not be necessary for every patient. USA study. Only patients with cancer were included in this analysis.

(c) Estimate used for the cost of treating major bleeding was not reported. Method for QALYs calculation: utilities not elicited from general population; health states descriptions used for the elicitation not reported; the possible survival benefit from LMWH was presented to the respondents before these results were confirmed; mortality was not included in the calculation. The time horizon was short.

(d) Study from Canada. Only patients with cancer were included in this analysis.

(e) Utilities for treatment were elicited from patients and not from the general public; as patient preferences might be influenced by clinical outcomes, including both intermediate outcomes and utilities directly elicited could lead to a double counting of QALY gain. Indirect costs were included in the analysis while they should be excluded. Source of funding not reported. The parameters tested in the PSA were limited. Outcomes unrelated to the strategies compared (vertebral fractures) were included in the analysis and a higher probability was assigned to the LMWH group. The mortality from PE was very high and probably refers to untreated patients.

(f) Study from Italy. Societal perspective was adopted (loss of income during hospital stay included).

(g) Cost of treating major bleeding was not included. Limited follow-up (no extrapolation to a longer time horizon). Small sample size.

(h) Study from Spain. No estimate of QALYs.

Table 48: LMWH vs VKA – Economic summary of findings

Study	Incremental cost (£)	Incremental effects (QALYs)	ICER (£/QALY)	Uncertainty
Aujesky 2005[10]	4,775 [(a)]	0.051 [(b)]	93,635	The results are very sensitive to the cost of LMWH. In the base case the daily drug cost was £40, in a threshold analysis LMWH was cost-effective using a willingness-to-pay of $50k/QALY if the daily drug cost was <£11. The current daily cost in the UK is £8.47 (BNF 60). LMWH was cost-effective if there was no need for home nursing (in the base case 20% patients needed this) and if the risk difference in early mortality between LMWH and VKA was >8%. PSA: VKA was cost-effective in 97% of the Monte Carlo iterations.
Dranitsaris 2006[59]	1,132 [(c)]	0.16 [(d)]	7,073	Worst-case/best-case scenario analysis using extreme differences in costs and QALYS showed a range of the ICER = £4,927/QALY - £11,008/QALY.
Marchetti 2001[154]	195 [(e)]	0.036 [(f)]	5,427	If recurrence of VTE after completion of therapy was included LMWH was not cost-effective anymore. Threshold analysis: LMWH was cost-effective up to a daily drug cost of £17. PSA (only risk of PE and major bleeding were tested): LMWH was cost-effective in 87% of the simulations. If the recurrence of VTE was included LMWH was cost-effective in 51% of the simulations.
Perez-de-llano 2010[185]	376 [(g)]	Not applicable [(h)]	Not applicable	

(a) Cost of drugs, monitoring visits, recurrent events (DVT, PE), and treatment of non-cerebral major bleeding. 2002 USD converted into GBP using the purchasing power parities.

(b) Calculated using baseline utility for cancer = 0.77, utility of permanent disability after intracranial bleeding = 0.60, disutilities of acute events equal to mean length of hospital stay (non-cerebral MB, DVT, PE). Assumptions: patients treated at home had half the disutility of patients treated in hospital. Minor bleeding led to 1 outpatient day lost.

(c) Cost of drugs, laboratory tests, unscheduled clinical visits, diagnostic tests relevant for VTE, blood transfusion, and major bleeding events. 2005 Canadian dollars converted into GBP using the purchasing power parities.

(d) Based on preference elicited from nurses and pharmacists through the description of clinical profiles of treatments (LMWH = 0.66, VKA = 0.34). Mortality was not included in the analysis. QALYs were calculated by dividing the preferences by 2 (6 months time horizon).

(e) Cost of drugs, blood tests, clinic appointments, supplies, cost of treating DVT, PE, severe post-thrombophlebitis syndrome, vertebral fracture, major bleeding, minor bleeding, stroke, loss of income during hospital stay. 2001 USD converted into GBP using the purchasing power parities[177].

(f) Treatment specific utilities elicited with a modified time trade-off method in 48 patients attending an anticoagulation clinic: LMWH = 0.992, VKA = 0.988. Utilities attached to stroke = 0.5 and post-thrombophlebitis syndrome = 0.96. For short-term adverse effects a one week toll was applied.

(g) Cost of hospital stay, outpatient visits, diagnostic tests, laboratory tests, study drugs, other resources. 2008 Euro converted into GBP using the purchasing power parities.

(h) Outcomes reported in the studies were symptomatic VTE events, adverse events and bleeding events. There were no statistically significant differences in any of the outcomes. See clinical evidence table for details of clinical results.

Patients with cancer

The two studies on patients with cancer[10,59] were based on the CLOT study,[138] included in our review. They reached different conclusions due to the dissimilarities in the modelling approaches. The study by Aujesky et al (2005)[10] was conducted in the USA and was built as a Markov model with lifetime extrapolation; the six month probabilities of death, major bleeding, minor bleeding and recurrent VTE were derived from the RCT and for the lifetime extrapolation the long-term survival of cancer patients with VTE was obtained from a retrospective cohort study. Quality of life values incorporated and attached to events and health states were:

- Baseline utility for cancer patients = 0.77
- Permanent disability after intracranial bleeding = 0.60
- Disutilities for acute complications = days of hospitalisation
- Disutility from treatment in hospital = 0.01
- Disutility from treatment at home = 0.005

In the conclusions, the authors discussed the lower cost of LMWH in the UK where this drug could be cost-effective (daily cost in the study was £40 while from the BNF60[111] it would be £8.47).

The other study by Dranitsaris et al (2006)[59] was conducted in Canada and was a decision model with a six month time-horizon. The method by which QALYs were calculated was different: the clinical profile of treatments from the RCT [138] was described to a sample of 24 oncology nurses and pharmacists with clinical experience. They used the time trade-off method to elicit their preferences over treatments with LMHW and warfarin. They attached these preferences to each strategy as follows:

- Utility in patients treated with warfarin = 0.34
- Utility in patients treated with LMWH = 0.66

Since the method used to calculate QALYs has considerable limitations, the conclusions should be used with caution.

Non-cancer patients

The study by Marchetti et al (2001)[154] was a decision model based on a meta-analysis in patients with DVT. Fifteen percent of the included population also had cancer and 20% had a previous VTE. The outcomes from the meta-analysis at three months (risk of DVT, PE and recurrence while on treatment, major and minor bleeding, stroke and post-thrombophlebitic syndrome) were extrapolated to a lifetime horizon. Utilities were attached only to stroke and post-thrombophlebitic syndrome while a one week toll was applied to the other short-term events. In addition to event-specific utilities, treatment-specific utilities were elicited from 48 patients attending an anticoagulation clinic and used to adjust baseline utility in patients with no events:

- Utility in patients treated with warfarin = 0.988
- Utility in patients treated with LMWH = 0.992

The analysis is likely to be biased against warfarin due to the baseline utility adjustment (which has methodological issues) and the inclusion of indirect costs. In addition, when the VTE recurrences after the end of the treatment were included in the analysis, LMWH was no longer cost-effective.

Perez-de-llano et al (2010)[185] estimated the cost of treatment strategies alongside an RCT included in our review (see 7.3.2.1) using a small cohort of patients (n=102) over six months. None of the clinical outcomes assessed was statistically significant (mortality, PE, recurrent VTE, major bleeding). There was a small difference in costs favouring VKA against LMWH (£5,368 vs £5,744) but this was not statistically significant.

7.3.2.3 Evidence statements

Clinical

In all patients with VTE: 16 studies in 2953 people showed that it is unlikely that there is any difference of clinical importance in all cause mortality between the LMWH group and VKA group (MODERATE QUALITY).

In the non cancer subgroup: 11 studies in 1538 people showed that it is uncertain whether there is a clinically important difference in all cause mortality between the LMWH group and VKA group (LOW QUALITY).

In the cancer subgroup: seven studies in 1415 people showed that it is uncertain whether there is a clinically important difference in all cause mortality between the LMWH group and VKA group (LOW QUALITY).

In all patients with VTE: five studies in 689 people showed that it is uncertain whether there is a clinically important difference in VTE related mortality between the LMWH group and VKA group (LOW QUALITY).

In all patients with VTE: 16 studies in 2916 people showed that there was a decrease which may be of clinical importance in the LMWH group compared to the VKA group for recurrent VTE rates (MODERATE QUALITY).

In the non cancer subgroup: 12 studies in 1772 people showed that it is uncertain whether there is a clinically important difference in recurrent VTE rates between the LMWH group and VKA group (LOW QUALITY).

In the cancer subgroup: five studies in 1144 people showed that there were clinically important fewer events in the LMWH group compared to the VKA group for recurrent VTE rates (MODERATE QUALITY).

In all patients with VTE: 15 studies in 2762 people showed that it is uncertain whether there is a clinically important difference in the number of people with major bleeding between the LMWH group and VKA group (LOW QUALITY).

In non cancer patients: 11 studies in 1607 people showed that there was a decrease of uncertain clinical importance in the LMWH group compared to the VKA group for major bleeding (LOW QUALITY).

In cancer patients: five studies in 1155 people showed that it is uncertain whether there is a clinically important difference in the number of people with major bleeding between the LMWH group and VKA group (LOW QUALITY).

Three studies in 445 people showed that it is very uncertain whether there is a clinically important difference in the number of people with fatal bleeding between the LMWH group and VKA group because the event rates were very low (VERY LOW QUALITY).

There were data from one study in 102 people for intracranial bleeding. No events were reported. The data could not be pooled (VERY LOW QUALITY).

One study in 165 people showed that it is very uncertain whether there is a clinically important difference in the number of people with PTS between the LMWH group and VKA group (VERY LOW QUALITY).

No studies reported quality of life as an outcome.

Economic	There is a high uncertainty around the cost-effectiveness of LMWH as a long-term treatment for patients with VTE. The results of the economic studies were sensitive to several parameters, including the cost of LMWH and the estimate of effectiveness.

7.4 Duration of anticoagulation

7.4.1 Introduction

The purpose of anticoagulation is to prevent recurrence of VTE and its consequences. However, the treatment carries a risk of bleeding. Therefore, anticoagulation should normally continue only if the risk of recurrent VTE, or its consequences, outweighs the risk of bleeding (or other adverse effects) due to anticoagulant therapy.

The two main issues that need to be addressed are: for how long does treatment need to be given; and whether it is possible to define a group of patients who should continue anticoagulation indefinitely.

Two factors which have been linked to the risk of recurrence, which is an important consideration in the extension of anticoagulation treatment, are:

1) Whether a VTE episode has been provoked. VTE can be provoked by transient, major clinical risk factors such as significant immobility, surgery, trauma, and pregnancy or puerperium. The GDG also considered the combined contraceptive pill and hormone replacement therapy to be provoking factors as it has been shown that these patients are at a lower risk of recurrence.[16] These provoking factors are identifiable, temporary and can be removed. Removal of a temporary risk factor reduces the risk of recurrent VTE, especially if the risk factor was surgery.[16] If a VTE occurs in the absence of major clinical risk factors, the patients should be considered as having an unprovoked VTE even if they have active cancer, thrombophilia or a family history of VTE, because these underlying risks will remain unchanged in the patient.

2) The initial presentation of VTE. Patients with an initial symptomatic PE are more at risk of recurrent VTE as a PE than patients who initially presented with DVT, and therefore are at increased risk of VTE related mortality.[15,165] The risk of recurrence, and morbidity or mortality in patients who presented with isolated calf vein DVT is less clear, and individuals need to be assessed on a case by case basis.[193] Current diagnostic strategies also do not specifically look for isolated calf vein DVT. Therefore, in the following question and meta-analysis of data, two important subgroups were considered and investigated whenever possible: (1) provoked vs unprovoked and (2) initial presentation of symptoms (PE vs proximal DVT).

Other risk factors associated with a recurrence of VTE among patients with an unprovoked initial episode have been a matter of debate. These include male sex[56,158,206] and possibly PTS[206,232] and a raised D-dimer after stopping anticoagulation.[182,255] The risk factors for recurrence were not investigated as part of the review.

7.4.2 What is the optimal treatment duration for pharmacological interventions?

a) **6 months vs 3 months**

b) **longer vs shorter duration of treatment**

Standard practice in the UK has been to give 3 or 6 months of treatment for a first VTE. Following this, a decision is made whether to continue treatment indefinitely. The GDG therefore decided to look at the evidence comparing 3 and 6 months of treatment. If there were no important differences

between these groups, it would be possible to group together data with these treatment durations (3 or 6 months) against a longer duration of treatment.

See clinical evidence tables in Appendix E.8.2 and forest plots in Appendix G.3.5.

7.4.2.1 Clinical evidence

There were important differences between the studies found for this clinical question:

- Different populations were enrolled, with potentially different risk of recurrences:
  - Provoked vs unprovoked VTE: 4 studies looked at first unprovoked VTE,[3,62,66,118] 1 study was of first episode of PE,[2] 2 studies included mixed populations with first or second VTE both provoked and unprovoked,[30,217] and 1 study consisted of patients with a second episode of VTE.[215]
  - Main presentation: PE or DVT, or a mixture of both.
  - First VTE vs recurrent or second VTE.
- Different lengths of duration of interventions and control between studies.
- Study design:
  - Different lengths of follow up between studies and between different arms within the same study. Some studies[2,3,66] follow up from randomisation up to a specified time after discontinuation of oral anticoagulation, resulting in shorter follow up time for the shorter treatment arm.
  - Randomisation occurred after an initial period of anticoagulation in 4 studies.[2,3,62,118]

For the purpose of our analysis, we subgrouped the populations with potentially different risk of recurrence.

Table 49: Longer vs shorter duration of oral anticoagulation – Summary of included studies

Study	Population (as described in the study)	Percentage PE (approximate)	Percentage unprovoked (approximate)	Longer duration (months)	Shorter duration (months)	Length of Follow-up
Agnelli 2001[3]	1st episode idiopathic proximal DVT	0	100	12	3[(c)]	2 years from discontinuation of oral anticoagulation
Agnelli 2003[2]	1st episode PE	100	56	6– temporary risk factor 12 - idiopathic	3[(c)]	2 years from discontinuation of oral anticoagulation
Kearon 1999[118]	1st episode idiopathic VTE [(a)]	25	100	3 (pre randomisation) + 24	3[(c)]	1 year (mean 10 months) post randomisation
Campbell 2007[30]	DVT or PE without persistent risk factor[(b)]	30	45	6	3	1 year post randomisation
Farraj 2004[66]	1st idiopathic VTE	30	100	24	6	1 year from discontinuation of oral anticoagulation
Eischer 2009[62]	1st	40	100	30	6[(c)]	2 years post

Study	Population (as described in the study)	Percentage PE (approximate)	Percentage unprovoked (approximate)	Longer duration (months)	Shorter duration (months)	Length of Follow-up
	spontaneous VTE with high factor VIII (>230 IU/dl)					randomisation + extended follow-up (total mean 37 months)
Schulman 1985[217]	1st DVT, unknown or permanent risk	0	Unclear	6	3	1 year post randomisation with plethysmography + varying additional clinical follow-up
	2nd DVT	0	Unclear	12	6	
Schulman 1997[215]	2nd VTE	15	Unclear (~19% temp risk factor, 7% cancer)	Indefinite	6	4 years post randomisation

(a) 5% had a previous episode of VTE due to transient risk factor.
(b) 3% had a personal (>3 years previously) or family history of VTE.
(c) Patients were randomised after successfully (without any events) completing 3 or 6 months of treatment, into the longer duration of treatment or treatment discontinuation.

Table 50: 6 months vs 3 months oral anticoagulation – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
VTE Recurrence[30,217]	2	RCT	Serious limitations [(a)]	No serious inconsistency[(b)]	No serious indirectness	Serious[(c)]
Major bleeding[30]	1	RCT	Serious limitations[(a)]	No serious inconsistency[(b)]	No serious indirectness	Serious[(c)]
All cause mortality[30,217]	2	RCT	Serious limitations [(a)]	No serious inconsistency[(b)]	No serious indirectness	Serious imprecision [(c)]
VTE related mortality[30,217]	2	RCT	Serious limitations[(a)]	No serious inconsistency[(b)]	No serious indirectness	Serious imprecision [(c)]
Fatal bleeding[30,217]	2	RCT	Serious limitations[(a)]	No serious inconsistency[(b)]	No serious indirectness	Very serious imprecision [(c)]
Intracranial bleeding[30]	1	RCT	Serious limitations [(a)]	No serious inconsistency[(b)]	No serious indirectness	Very serious imprecision [(c)]
PTS	0	-	-	-	-	-
Quality of life	0	-	-	-	-	-

(a) Open label design (not blinding participants, investigators and outcomes assessors),[30,217] prolonged/more intensive follow up of the intervention arm.[217]
(b) All analysed using random effects analysis. This was used because of the heterogeneous population and different lengths of anticoagulation treatment and follow up.
(c) CIs are wide and crossed default MID.

Table 51: 6 months vs 3 months oral anticoagulation - Clinical summary of findings

Outcome	6 months	3 months	Relative risk (95% CI)	Absolute effect	Quality
VTE Recurrence	28/400 (7%)	32/389 (8.2%)	RR 0.85 (0.52 to 1.39)	12 fewer per 1000 (from 39 fewer to 32 more)	LOW
Major bleeding	8/380 (2.1%)	0/369 (0%)	RR 16.51 (0.96 to 285)	-	LOW
All cause mortality	21/400 (5.3%)	17/389 (4.4%)	RR 1.2 (0.64 to 2.24)	9 more per 1000 (from 16 fewer to 54 more)	LOW
VTE related mortality	3/400 (0.8%)	3/389 (0.8%)	RR 1.02 (0.22 to 4.8)	0 more per 1000 (from 6 fewer to 29 more)	LOW
Fatal bleeding	2/400 (0.5%)	0/389 (0%)	RR 4.86 (0.23 to 100.8)	-	VERY LOW
Intracranial bleeding	1/380 (0.3%)	0/369 (0%)	RR 2.91 (0.12 to 71.29)	-	VERY LOW

The results presented here were conducted using random effects analysis, because of the concern about the heterogeneous population and different lengths of anticoagulation treatment and follow up. This is a more conservative analysis but all analyses were also tested with fixed effects analysis where appropriate and any significant change between the two methods would have been discussed.

Table 52: Longer vs shorter duration of oral anticoagulation – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
VTE Recurrence[2,3,30,62,66,118,215,217]	8	RCT	Serious limitations[(a)]	No serious inconsistency[(b)]	No serious indirectness	Serious imprecision[(c)]
Subgroup: 1st episode[30,217]	*2*	*RCT*	*Serious limitations[(a)]*	*No serious inconsistency[(b)]*	*No serious indirectness*	*Serious imprecision[(c)]*
Subgroup: 1st episode unprovoked[2,3,62,66,118]	*5*	*RCT*	*Serious limitations[(a)]*	*No serious inconsistency[(b)]*	*No serious indirectness*	*Serious imprecision[(c)]*
Subgroup: 2nd episode[215,217]	*2*	*RCT*	*Serious limitations[(a)]*	*No serious inconsistency[(b)]*	*No serious indirectness*	*Serious imprecision[(c)]*
Major bleeding[2,3,30,62,66,118,215]	7	RCT	Serious limitations[(a)]	No serious inconsistency[(b)]	No serious indirectness	No serious imprecision
All cause mortality[2,3,30,66,118,215,217]	7	RCT	Serious limitations[(a)]	No serious inconsistency[(b)]	No serious indirectness	Serious imprecision[(c)]
VTE related mortality[2,3,30,66,118,215,217]	7	RCT	Serious limitations[(a)]	No serious inconsistency[(b)]	No serious indirectness	Serious imprecision[(c)]
Fatal bleeding[2,3,30,62,66,118,215]	7	RCT	Serious limitations[(a)]	No serious inconsistency[(b)]	No serious indirectness	Serious imprecision[(c)]

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Intracranial bleeding[2,3,30,62,66,118,215]	7	RCT	Serious limitations[(a)]	No serious inconsistency[(b)]	No serious indirectness	Serious imprecision[(c)]
PTS	0	-	-	-	-	-
Quality of life	0	-	-	-	-	-

(a) Studies used different definitions of lengths of follow up - some studies followed up patients for a defined period from end of treatment,[2,3,66] this has a risk of bias favouring the arms with shorter duration of treatment since the overall duration where events are measured are shorter. Other limitations included open label design (not blinding participants, investigators and outcomes assessors,)[30,66,217] prolonged/more intensive follow up of the intervention arm,[62,217] all patients given stockings for at least one year.[215]

(b) All analysed using random effects analysis. This was used because of the heterogeneous population and different lengths of anticoagulation treatment and follow up.

(c) CIs are wide and crossed default MID.

Table 53: Longer vs shorter duration of oral anticoagulation - Clinical summary of findings

Outcome	Longer duration	Shorter duration	Relative risk (95% CI)	Absolute effect	Quality
VTE Recurrence	74/953 (7.8%)	121/936 (12.9%)	RR 0.57 (0.34 to 0.97)	56 fewer per 1000 (from 4 fewer to 85 fewer)	LOW
Subgroup:1st episode	*28/400 (7%)*	*32/389 (8.2%)*	*RR 0.85 (0.52 to 1.39)*	*12 fewer per 1000 (from 39 fewer to 32 more)*	*LOW*
Subgroup: 1st episode unprovoked	*42/427 (9.8%)*	*65/426 (15.3%)*	*RR 0.63 (0.32 to 1.24)*	*56 fewer per 1000 (from 104 fewer to 37 more)*	*LOW*
Subgroup: 2nd episode	*4/126 (3.2%)*	*24/121 (19.8%)*	*RR 0.25 (0.04 to 1.75)*	*149 fewer per 1000 (from 190 fewer to 149 more)*	*LOW*
Major bleeding	31/923 (3.4%)	8/906 (0.9%)	RR 2.83 (1.34 to 5.97)	16 more per 1000 (from 3 more to 44 more)	MODERATE
All cause mortality	52/936 (5.6%)	51/919 (5.5%)	RR 0.99 (0.68 to 1.45)	1 fewer per 1000 (from 18 fewer to 25 more)	LOW
VTE related mortality	5/846 (0.6%)	6/919 (0.7%)	RR 0.96 (0.32 to 2.84)	0 fewer per 1000 (from 4 fewer to 12 more)	LOW
Fatal bleeding	4/923 (0.4%)	3/906 (0.3%)	RR 1.31 (0.23 to 7.33)	1 more per 1000 (from 3 fewer to 21 more)	LOW
Intracranial bleeding	2/923 (0.2%)	3/906 (0.3%)	RR 0.7 (0.14 to 3.6)	1 fewer per 1000 (from 3 fewer to 9 more)	LOW

The results presented here were conducted using random effects analysis, because of the concern about the heterogeneous population and different lengths of anticoagulation treatment and follow up. This is a more conservative analysis but all analyses were also tested with fixed effects analysis where appropriate and any significant change between the two methods would have been discussed.

7.4.2.2 Economic evidence

One study[12] was found which compared different durations of anticoagulant treatment after a first idiopathic VTE (3 months, 6 months, 12 months, 24 months and unlimited duration). This study was excluded because it had potentially serious limitations and partial applicability, particularly when compared to the original economic model that was built by the NCGC (see Appendix I).

In fact, the economic analysis in this study[12] was conducted in the USA where the cost of anticoagulant treatment is considerably higher compared to the UK (they estimated a cost of about £789 per year vs. our estimate of £147 per year). No separate analysis was conducted for patients with an initial PE or DVT and sensitivity analyses were conducted only on the basis of age and sex. From the paper it was unclear how the clinical parameters were obtained from the cited references. In addition, the analysis was conducted from a societal perspective (indirect costs were included).

This area was identified as very important for economic evaluation given the uncertainty over the trade-off between cost, effectiveness and adverse events of long-term treatment. Therefore an original economic model was built to answer this question.

Please see cost- effectiveness analysis in Appendix I for further details.

Health economic modelling

a) Model overview/methods

The economic evaluation was a cost-utility analysis, where lifetime costs and quality-adjusted life-years (QALYs) were calculated from a UK NHS and personal social services perspective.

The comparison with a 6-month treatment was deemed unnecessary as from our clinical review this strategy did not show any additional benefit compared to a 3-month treatment. The model compared two strategies after the initial 3-month treatment: in the 'no long-term treatment' strategy patients interrupt treatment unless they have a VTE recurrence, in which case they have indefinite long-term treatment. In the other strategy 'long-term treatment', patients are treated indefinitely unless they have an episode of major bleeding, in which case they stop treatment. Two separate analyses were conducted for patients with an initial DVT and patients with an initial PE.

Outcomes considered in the model were: VTE recurrences, proportion of VTE recurrences as PE, mortality from PE, major bleeding risk including stroke. These events were associated with consequences in terms of costs and quality of life. The baseline risks of events were obtained from different sources.[15,57,145,184]while the relative risk of treatment vs no treatment was derived from our review of clinical effectiveness. From the included studies we selected those where patients who had VTE were followed up after the initial three months of standard treatment as the question we wished to assess was whether at that particular time point treatment should be stopped or continued. Three papers corresponded to these criteria.[2,3,118] However, the study by Agnelli et al (2003)[2] was excluded because the population was a mix of unprovoked and provoked VTE. Kearon et al (1999)[118] was also excluded because it had a shorter follow-up time compared to Agnelli et al (2001)[3]. Therefore, relative risks of recurrence and major bleeding were obtained from Agnelli et al (2001).[3]

b) Results

The base case results show that long-term treatment in patients with an initial DVT is not cost-effective; however, long-term treatment in patients with an initial PE is cost-effective (see Table 54). In both groups extending treatment generates more QALYs and increases costs compared to interrupting treatment after the first three months; however, while the increase in costs represents good value-for-money in the group of patients with an initial PE (ICER = £9,601/QALY, below the £20,000/QALY threshold), this is increase is not justified by the smaller increment in QALYs in the group of patients with an initial DVT (ICER=£79,758/QALY, above the £20,000/QALY threshold).

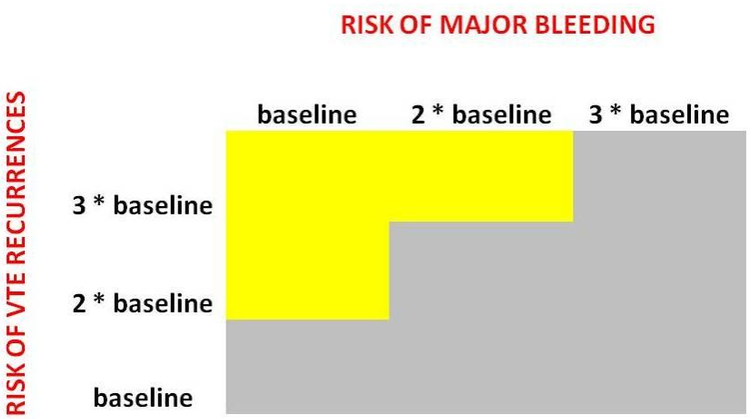
Table 54: Base case cost-effectiveness results (probabilistic)

	Strategy	Cost (£)	Incremental Cost (£)	QALYs	Incremental QALYs	ICER (£/QALY)
Initial PE	No long-term treatment	1,809		12.3620		
	Long-term treatment	3,479	1,671	12.5360	0.1740	9,601
Initial DVT	No long-term treatment	1,975		12.5910		
	Long-term treatment	3,490	1,515	12.6100	0.0190	79,758

Results are dependent on the two major events incorporated in the model: VTE recurrences and major bleeding. In a two-way sensitivity analysis we changed the baseline risk of recurrences (baseline risk changed by the same proportion in first and following years) and the risk of major bleeding.

In the group of patients with initial DVT (Figure 4) long-term treatment is cost-effective only for those patients with an increased risk of VTE recurrence and with no increased risk of major bleeding. For example, in patients with twice the baseline risk of VTE recurrence long-term treatment is cost-effective if there is no increase in the risk of major bleeding. However, long-term treatment is not cost-effective if patients have risk factors that put them at an increased risk of major bleeding. We also performed a threshold analysis by keeping the risk of major bleeding equal to the baseline used in the model (1.77% per year) and varying the risk of VTE recurrences. According to this analysis, long-term treatment is cost-effective if the risk of VTE recurrences is at least 1.6 times the baseline risk (e.g. in the first year 1.6 *8.4% = 13.4%; in subsequent years =1.6*5.8% = 9.3%).

Figure 4 - Two-way sensitivity analysis in patients with initial DVT - risk of VTE recurrences vs risk of major bleeding.



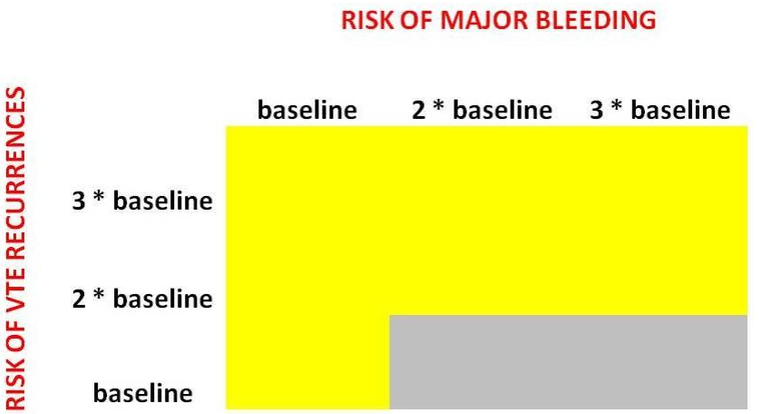
The yellow-shaded area is where long-term treatment is cost-effective; the grey area is where it is not cost-effective. Baseline risk of VTE recurrences is 8.4% in the first year and 5.8% in the following years; baseline risk of major bleeding is 1.77% per year.

In the group of patients with initial PE (

Figure **5 - Two-way sensitivity analysis in patients with initial PE - risk of VTE recurrences vs risk of major bleeding.**

) long-term treatment is always cost-effective unless the risk of major bleeding is increased. For example, long-term treatment is cost-effective for patients in whom the risk of major bleeding is twice the baseline only if the risk of VTE recurrence is also at least twice the baseline. However it is not cost-effective if patients do not have risk factors that put them at an increased risk of VTE recurrence. We also conducted a threshold analysis by keeping the risk of VTE recurrences equal to the baseline and varying the risk of major bleeding. Long-term treatment is cost-effective if the risk of major bleeding is less than 1.8 times the baseline risk (i.e. 1.8 *1.77% = 3.2%).

Figure 5 - Two-way sensitivity analysis in patients with initial PE - risk of VTE recurrences vs risk of major bleeding.



The yellow-shaded area is where long-term treatment is cost-effective; the grey area is where it is not cost-effective. Baseline risk of VTE recurrences is 7.4% in the first year and 5.0% in the following years; baseline risk of major bleeding is 1.8% per year.

The model has the following limitations: it is based on limited clinical evidence (only one RCT for the estimate of effectiveness) and there could be some heterogeneity in the population of the studies informing different parameters. For example, the estimate of the treatment effectiveness was obtained from patients with a first idiopathic proximal DVT while the baseline risk of recurrences was obtained from patients with unprovoked VTE or VTE caused by reversible risk factors. The risk of major bleeding while on treatment was obtained from a slightly different population (patients treated with anticoagulants for nonrheumatic atrial fibrillation). In addition, the model required a lifetime extrapolation on short-term data.

The results including the two-way sensitivity analyses are difficult to interpret from a clinical point of view as at the moment there are no validated scores to calculate both the risk of VTE recurrences and the risk of major bleeding. However, based on recent studies[56,158,182,206,232,255] some risk factors such as sex, PTS, and perhaps D-dimer have been identified as relevant to refine the individual risk of VTE recurrence.

7.4.2.3 Evidence statements

Clinical

6 vs 3 months

Two studies in 789 people showed that it is very uncertain whether there is a clinically important difference in VTE recurrence between the 6 month group and the 3 month group (LOW QUALITY).

One study in 749 people showed that there is a likely increase in major bleeding which may be of clinical importance in the 6 month group compared to the 3 month group, but it is uncertain whether this difference is clinically important because of the event rate was low (LOW QUALITY).

Two studies in 789 people showed that it is very uncertain whether there is a clinically important difference in all cause mortality between the 6 month group and the 3 month group (LOW QUALITY).

Two studies in 789 people showed that it is it is uncertain whether there is a clinically important difference in VTE recurrence between the 6 month group and the 3 month group (LOW QUALITY).

Two studies in 789 people showed that it is very uncertain whether there is a clinically important difference in fatal bleeding between the 6 month group and the 3 month group (VERY LOW QUALITY).

One study in 749 people showed that that it is very uncertain whether there is a clinically important difference in intracranial bleeding between the 6 month group and the 3 month group because the number of events reported was very low (VERY LOW QUALITY).

No studies reported PTS or quality of life as an outcome.

Longer vs shorter duration

In all VTE patients: eight studies in 1889 people showed that there is a decrease of uncertain clinical importance in the longer duration group compared to the shorter duration group for VTE recurrence (LOW QUALITY).

In the first episode of VTE subgroup: two studies in 789 people showed that it is very uncertain whether there is a clinically important difference in VTE recurrence between the longer duration group and the shorter duration group (LOW QUALITY).

In the first episode of unprovoked VTE subgroup: five studies in 853 people showed that it is very uncertain whether there is a clinically important difference in VTE recurrence between the longer duration group and the shorter duration group (LOW QUALITY).

In the second episode of VTE subgroup: two studies in 247 people showed that it is very uncertain whether there is a clinically important difference in VTE recurrence between the longer duration group and the shorter duration group (LOW QUALITY).

Seven studies in 1829 people showed that there is an increase which may be of clinical importance in the longer duration group compared to the shorter duration group for major bleeding (MODERATE QUALITY).

Seven studies in 1855 people showed that it is very uncertain whether there is a clinically important difference in all cause mortality between the longer duration group and the shorter duration group (LOW QUALITY).

Seven studies in 1765 people showed that it is very uncertain whether there is a clinically important difference in VTE related mortality between the longer duration group and the shorter duration group (LOW QUALITY).

Seven studies in 1829 people showed that it is very uncertain whether there is a clinically important difference in fatal bleeding between the longer duration group and the shorter duration group (LOW QUALITY).

Seven studies in 1829 people showed that it is very uncertain whether there is a clinically important difference in intracranial bleeding between the longer duration group and the shorter duration group (LOW QUALITY).

No studies reported PTS or quality of life as an outcome.

Economic

The cost-effectiveness of long-term treatment depends on the type of initial VTE episode, the risk of VTE recurrence and the risk of major bleeding. In patients after an initial unprovoked PE episode, long-term treatment is cost-effective unless the risk of major bleeding is increased. In patients after an initial unprovoked DVT episode, it is not cost-effective unless the risk of VTE recurrence is increased and the risk of major bleeding is not elevated.

7.5 Recommendations and link to evidence

Recommendations	**15. Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:** • **For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.** • **For patients with an increased risk of bleeding consider UFH.** • **For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 21 and 22).** **Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 17) is 2 or above for at least 24 hours, whichever is longer.**
Relative values of different outcomes	All cause mortality, VTE related mortality, and recurrent VTE and major bleeding were considered the most important outcomes. The other important outcomes were: intracranial bleeding, fatal bleeding, quality of life, PTS and heparin induced thrombocytopenia (HIT).
Trade off between clinical benefits and harms	Reduction in VTE related mortality and recurrent VTE were considered against major bleeding occurrences, including intracranial bleeding and fatal bleeding. No RCT evidence was available for important longer term outcomes such as PTS and quality of life and it is uncertain whether there are any important differences between these intervention options. The specific tradeoffs between each intervention option are summarised below: **LMWH vs UFH** Overall, the meta-analysis showed that LMWH had more favourable outcomes than UFH, in both benefits and harms from treatment. There were fewer deaths and recurrent VTE in the LMWH group compared to the UFH group, and also less major bleeding. The rates of HIT were similar (about 0.4%) in both arms. **LMWH vs fondaparinux** There were no observed differences in major bleeding and recurrent VTE outcomes, but it is very uncertain whether the patients on fondaparinux have a higher mortality rate (all cause, and fatal bleeding); the CIs for the relative risks were very wide for these outcomes, but the difference in absolute rates is low. Evidence was only available for DVT patients for this comparison. There were no data for safety and efficacy of fondaparinux compared to LMWH in patients with PE. **Fondaparinux vs UFH**

Recommendations	**15. Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:** • **For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.** • **For patients with an increased risk of bleeding consider UFH.** • **For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 21 and 22).** **Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 17) is 2 or above for at least 24 hours, whichever is longer.**
	There might be some advantages in using fondaparinux compared to UFH; major bleeding and recurrent VTE rates may be lower, particularly in patients with cancer. However, it is uncertain whether the patients on fondaparinux have a higher mortality rate (all cause, and fatal bleeding); the CIs were very wide for these outcomes and the difference in absolute rates is low. However, data were only available from one study conducted only in patients with PE. There were no data for safety and efficacy of fondaparinux compared to LMWH in patients with proximal DVT. **Overall comparison between LMWH, UFH and fondaparinux** There was more evidence available for LMWH compared to UFH, and it showed that LMWHs generally have a slight advantage over UFH in all outcomes considered. However, the benefits vs harms of fondaparinux vs LMWH are less clear. There were also no data in PE patients for this comparison. The only study which compared these two interventions used a LMWH dose which is higher than UK dose, making it particularly hard to draw a firm conclusion and interpret the slightly increased fatal bleeding and all cause mortality rate, particularly when the CIs are very wide. **Patients with renal problems or haemodynamically unstable PE** UFH, which has a shorter half life, may have an advantage in patients with renal impairment because there is less risk of accumulation of the drug. The effect can be more quickly reversed, and therefore it is considered a better option if there is an uncertain risk of bleeding, such as when thrombolysis or surgery may be required. It is also the only licensed product for patients with PE who are haemodynamically unstable. **Starting treatment as soon as possible** It is important that parenteral anticoagulation is achieved quickly for patients with VTE in order to reduce the risk of clot propagation or further embolic events.

Recommendations	**15. Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:** • **For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.** • **For patients with an increased risk of bleeding consider UFH.** • **For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 21 and 22).** **Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 17) is 2 or above for at least 24 hours, whichever is longer.**
Economic considerations	The economic evidence shows that LMWH is more cost-effective or cost-saving compared to UFH as a short-term treatment for PE or DVT. This conclusion is reinforced if more patients are treated with LMWH as outpatients. No evidence was found on fondaparinux; a simple cost analysis considering only the acquisition costs shows that the average treatment with fondaparinux is more costly compared to LMWH and UFH. Since some hospitals might be able to obtain the different products at different costs, and since the clinical review did not show any difference between fondaparinux and LMWH, they could both be viable options based on local costs.
Quality of evidence	Direct comparisons were available for all three groups of pharmacological agents available for the initial anticoagulation of VTE: LMWH vs UFH, fondaparinux vs UFH and fondaparinux vs LMWH, but not for both patients with PE and DVT. All studies excluded patients at increased risk of bleeding, and there was no specific evidence for patients with increased risk of bleeding, renal impairment or haemodynamically unstable PE. **LMWH vs UFH** For LMWH compared to UFH the quality of evidence was low for most outcomes, despite the abundance of RCTs in this area. For studies comparing LMWH and UFH, there were some limitations in the design of studies. Many of these studies were published more than ten years ago, and there were some concerns about studies which were not using the doses of heparin currently licensed in the UK. There were also variations in the definition of "bleeding" and potential publication bias. Outcomes such as fatal bleeding, intracranial bleeding and VTE related deaths were not consistently reported. Quality of life data were only reported by one study, and it was uncertain whether the instrument was validated. There was no reported data for frequency of HIT in the studies reviewed. **Fondaparinux** Only two studies were found for fondaparinux. One compared fondaparinux vs UFH in patients with PE, while the other compared fondaparinux with LMWH

Recommendations	**15. Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:** • **For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.** • **For patients with an increased risk of bleeding consider UFH.** • **For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 21 and 22).** **Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 17) is 2 or above for at least 24 hours, whichever is longer.**
	in patients with DVT. The quality of evidence was low. Although these trials are relatively large, these were still serious imprecision for most of the outcomes. The fondaparinux vs UFH comparison also had serious study limitations (unclear allocation concealment and randomisation procedure). There was a subgroup analysis for patients with cancer in the study comparing against UFH, suggesting that in this subgroup there may be a lower risk of VTE recurrence or bleeding in patients treated with fondaparinux. The economic evidence has potentially serious limitations and partial applicability.
Other considerations	In addition to the clinical evidence available, the GDG also discussed important practical advantages of using LMWH and fondaparinux over UFH. • LMWH or fondaparinux are administered by subcutaneous injections, while UFH is usually administered by continuous intravenous infusions. Because a cannula is inserted for the UFH infusion, patients are at risk of vascular access related problems (such as local infections and bacteraemia). Not being attached to an infusion device also promotes mobility and patient independence. • Patients on LMWH or fondaparinux do not require APTT monitoring. With these advantages, patients on LMWH or fondaparinux often have a shorter hospital stay than patients receiving UFH. Use of LMWH or fondaparinux could also facilitate the option of outpatient initial management of DVT and haemodynamically stable PE in some patients. The GDG noted that it is very important to consider the individual patient circumstances, such as comorbidities and contraindications in order to offer the most suitable agent for the patient. Important considerations include: • **Renal status:** Dose adjustment and monitoring may be required as patients with renal impairment may accumulate excessive amounts of these drugs in the body. LMWH and fondaparinux should be used with caution for people with renal impairment, and UFH should be considered as an alternative. UFH

Recommendations	**15. Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:** • **For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.** • **For patients with an increased risk of bleeding consider UFH.** • **For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 21 and 22).** **Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 17) is 2 or above for at least 24 hours, whichever is longer.**
	has a short half-life and is predominantly metabolised in the liver compared to LMWHs that are predominantly excreted through the kidneys. UFH therefore may be more suitable for patients who are at risk of bleeding or have renal impairment. • **Risk of bleeding or need for surgery or thrombolysis:** As in renal impairment patients, UFH is an alternative option for patients with uncertain risk of bleeding or if the patient may have to undergo surgical procedures or thrombolysis. Unfractionated heparin has a shorter half life and is more easily reversed if required. • **Risk of HIT:** Although the review did not show any difference between LMWH and UFH in the risk of heparin induced thrombocytopenia (HIT), the quality of evidence is very low. However, the GDG considered that there may be a lower risk of HIT in people receiving LMWH compared to UFH based on their clinical experience. However, if the patient has a history of HIT, fondaparinux is an alternative option because it is a synthetic pentasaccharide and not associated with HIT. • **Appropriate dose:** Dosing errors in administering LMWH to patients have been the subject of a National Patient Safety Agency alert (NPSA Rapid Response Report 14[170]); doses were frequently not adjusted to the appropriate clinical indication, weight or renal function. Patients should be weighed prior to receiving LMWH to ensure that they are prescribed the correct dose, especially in obese patients. Renal function should also be considered in all patients, although renal function testing should not delay the first dose it should be taken into account for subsequent doses. • **Patient preferences:** Both UFH and LMWH are of porcine origin. This may be a concern to some patients. If this is a concern, fondaparinux may be considered as a suitable alternative for some of these patients. • **Route of administration for UFH:** Both the intravenous route and the subcutaneous route were included for UFH in the evidence review. However, the main group of patients where UFH is likely to be used are those with risk of bleeding or accumulation due to severe renal impairment. The intravenous route has advantages over the subcutaneous route in patients

Recommendations	**15. Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:** • **For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.** • **For patients with an increased risk of bleeding consider UFH.** • **For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 21 and 22).** **Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 17) is 2 or above for at least 24 hours, whichever is longer.**
	where accumulation or bleeding may be problematic. If problems arise, the action of UFH can be limited by turning off the infusion. Protamine sulphate can be administered as indicated. LMWH and fondaparinux are not licensed for the treatment of haemodynamically unstable PE. These patients may also undergo thrombolysis (and therefore may be at a higher bleeding risk) and so only UFH is recommended for these patients. The recommendation emphasises that treatment is started as soon as possible. It is important that parenteral anticoagulation is achieved quickly for patients with VTE in order to reduce the risk of clot propagation or further embolic events. Initial treatment should be commenced without delay in patients diagnosed with DVT/PE and if necessary even prior to the confirmation of the diagnosis by imaging. As oral VKAs may take a few days to reach a level which is effective for anticoagulation, it is important to continue the initial parenteral treatment with heparins for fondaparinux until the INR is 2 or above for at least 24 hours, or 5 days, whichever is longer. This is to ensure adequate anticoagulation at all times. The GDG also noted that there are wide variations in the purchasing costs between various NHS organisations for LMWH and fondaparinux. Some organisations may be able to obtain fondaparinux at an equivalent or lower cost than LMWH, and this could be a consideration in the choice of agents. The GDG have prioritised this recommendation as a key priority for implementation. They considered that: it has a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes patient

Recommendations	**15. Offer a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs, with the following exceptions:** • **For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.** • **For patients with an increased risk of bleeding consider UFH.** • **For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy (see recommendations 21 and 22).** **Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]; see recommendation 17) is 2 or above for at least 24 hours, whichever is longer.**
	choice, promotes equalities and means patients reach critical points in the care pathway more quickly. Linked recommendations: Thrombolytic recommendations in section 8.2 and 0. Recommendations 3 and 5 in the DVT diagnosis chapter 5 and recommendations 11 and 13 in the PE diagnosis chapter 6. Recommendation 30 in the patient information chapter 11 which refers to LMWH being of porcine origin.

Recommendations	**16. Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months[(a)]. At 6 months, assess the risks and benefits of continuing anticoagulation[(b)].** **(a) At the time of publication (June 2012) some types of LMWH do not have UK marketing authorisation for 6 months of treatment of DVT or PE in patients with cancer. Prescribers should consult the summary of product characteristics for the individual LMWH and make appropriate adjustments for severe renal impairment or established renal failure. Informed consent for off-label use should be obtained and documented. (b) Although this use is common in UK clinical practice, at the time of publication (June 2012), none of the anticoagulants has a UK marketing authorisation for the treatment of DVT or PE beyond 6 months for patients with cancer. Informed consent for off-label use should be obtained and documented.**
Relative values of different outcomes	The GDG considered recurrent VTE, mortality and major bleeding as the most important outcomes. The other important outcome was quality of life.
Trade off between clinical benefits and harms	Reduction in recurrent VTE was considered against major bleeding occurrences, including intracranial bleeding and fatal bleeding. In patients with cancer, the evidence suggests that anticoagulation for 6 months with LMWH leads to better outcomes compared to switching to a VKA after initial LMWH treatment. There was an important reduction of recurrent VTE in patients who had used LMWH compared to VKA when these were given over 6 months in patients with cancer. The treatment has an overall benefit compared to VKA; all cause mortality and major bleeding were similar for both groups. It is uncertain whether there are any important differences in the quality of life of patients as no studies included this as an outcome. The option for initial treatment is less clear, as fondaparinux seemed to be favourable compared to UFH in cancer patients with PE, but there was no direct comparison with LMWH in cancer patients.
Economic considerations	Data from economic analyses suggest that use of LMWH instead of VKA is cost-effective. As LMWHs are associated with increased costs we would need additional certainty around their cost-effectiveness to recommend them for all patients. Economic studies have shown results to be sensitive to changes in parameters including costs and effectiveness estimates. Since there is stronger evidence of additional benefits of LMWH in patients with cancer, the GDG believe this intervention is likely to be more cost-effective in this group of patients.
Quality of evidence	The overall quality of evidence was moderate or low. One study, Lee 2003,[138] contributes to most of the information about the comparison. Data were only available up to 6 months and only for patients with proximal DVT or PE. The economic evidence has partial applicability and potentially serious limitations.
Other considerations	The evidence suggested that using LMWH instead of VKAs offered an overall benefit, for patients with proximal DVT or PE and active cancer. However, this means that patients will be having daily subcutaneous injections instead of taking oral tablets. Therefore, patient preference and practicalities, such as whether patients can reliably self-inject or have a carer (such as a relative or district nurse) to help to administer the injection needs to be taken into account. The ability of patients to adhere to the treatment plan is important for its success. The GDG was concerned that the cost of nurse-delivered injections may limit the availability of this service being available on the NHS and some VTE patients with active cancer may not be offered LMWH. If this is the case, there would be a serious equality of access issue. Patients who need support from

Recommendations	**16. Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months[(a)]. At 6 months, assess the risks and benefits of continuing anticoagulation[(b)].** **(a) At the time of publication (June 2012) some types of LMWH do not have UK marketing authorisation for 6 months of treatment of DVT or PE in patients with cancer. Prescribers should consult the summary of product characteristics for the individual LMWH and make appropriate adjustments for severe renal impairment or established renal failure. Informed consent for off-label use should be obtained and documented. (b) Although this use is common in UK clinical practice, at the time of publication (June 2012), none of the anticoagulants has a UK marketing authorisation for the treatment of DVT or PE beyond 6 months for patients with cancer. Informed consent for off-label use should be obtained and documented.**
	nurses and carers should still be offered the LMWH option, and the practicalities of these need to be discussed with them. In the study of using LMWH in cancer patients[138], 22% had nurse assistance for injection and only 6% withdrew in the LMWH group, indicating that this is a feasible option for a majority of patients, and should be offered based on the clinical benefits observed in clinical trials for this patient group. Arrangements should be in place for training of patients or carers in the technique of administration of LMWH in order to limit the numbers who require nurse-delivered injections. At 6 months, the need to continue anticoagulation should be reassessed and discussed with the patient. The current recommendation of international guidelines and UK clinical practice is to continue anticoagulation lifelong in patients with active cancer, based on expert clinical experience, case series and opinion, in the absence of randomised controlled trials[122]. Therefore, we have made a high priority research recommendation in this area (see research recommendations, section 7.6). Apart from the availability of evidence to support using LMWH instead of VKA in patients with cancer, the GDG also discussed the potential advantages based on their clinical experience: • It is difficult to maintain good INR control (which puts patients at risk of bleeding or more VTE events) while patients are on chemotherapy. This makes it a strong case for the use of LMWH for those patients with new VTE, and active cancer, particularly if undergoing chemotherapy. • Patients with cancer have a higher risk of major bleeding on anticoagulation compared to patients without cancer, which may relate to the underlying cancer and propensity for bleeding (e.g. ulcerated gastric cancer). • Patients with impaired renal function can receive LMWH at a reduced dose, and would therefore not be excluded. There may be an additional cost to Factor X monitoring for such patients, however probably few actual tests need to be conducted when patients are stabilised. For the purpose of this recommendation, the GDG considered the evidence available and defined active cancer as: receiving active anti-mitotic treatment; or was diagnosed within last 6 months; or recurrent or metastatic; or where the cancer is inoperable. This definition excludes squamous skin cancer and basal cell carcinoma (BCC). The GDG have prioritised this recommendation as a key priority for implementation as they considered that it has a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes patient

Recommendations	**16. Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for 6 months[(a)]. At 6 months, assess the risks and benefits of continuing anticoagulation[(b)] .** **(a) At the time of publication (June 2012) some types of LMWH do not have UK marketing authorisation for 6 months of treatment of DVT or PE in patients with cancer. Prescribers should consult the summary of product characteristics for the individual LMWH and make appropriate adjustments for severe renal impairment or established renal failure. Informed consent for off-label use should be obtained and documented. (b) Although this use is common in UK clinical practice, at the time of publication (June 2012), none of the anticoagulants has a UK marketing authorisation for the treatment of DVT or PE beyond 6 months for patients with cancer. Informed consent for off-label use should be obtained and documented.**
	choice, promotes equalities and means patients reach critical points in the care pathway more quickly. The potential equalities issues of access to this intervention for patients who are unable to self inject was discussed and documented above.

Recommendations	**17. Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment (see recommendations 18**Error! Reference source not found. **and 19).**
Relative values of different outcomes	The GDG considered all cause mortality the most important outcome. The other important outcomes include recurrent VTE, major bleeding (including fatal bleeding and intracranial bleeding) , VTE related mortality, quality of life and PTS were also important considerations
Trade off between clinical benefits and harms	The benefit of preventing recurrent VTE and deaths was considered against the risk of bleeding and its complications, including deaths. Of the two options available for longer term anticoagulation (VKA and LMWH), there is potentially improved VTE related mortality in patients without cancer on VKA. The risks of recurrences were lower in the group with LMWH, particularly for patients with cancer, but this benefit seems to be smaller and more uncertain for patients without cancer. The risk of major bleeding may also be lower in the group for LMWH. Treating patients for 6 months showed no increased benefits for lowered recurrent VTE (recurrences mostly occur after stopping treatment) when followed up for 1 year, but the increased risk bleeding may be important. For patients with provoked first episode proximal DVT or PE, it is unlikely that there are additional benefits of extending the treatment. Therefore, all patients with proximal DVT or PE should have 3 months of VKA, but the decision to continue beyond 3 months needs to be evaluated based on the individual's risk of recurrences compared to risk of bleeding.
Economic considerations	As LMWHs are associated with increased costs we would need additional certainty around their cost-effectiveness to recommend them for the patients. Economic studies have shown results to be sensitive to changes in parameters including costs and effectiveness estimates. Since there is stronger evidence of additional benefits of LMWH in patients with cancer, the GDG believe this

Recommendations	**17. Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment (see recommendations 18**Error! Reference source not found. **and 19).**
	intervention is likely to be more cost-effective in this group of patients. The GDG also discussed the level of resources that would be required with the use of warfarin in the community. Based on their experience, using warfarin in the community requires a district nurse to visit the patient and perform INR testing. A blood sample is also taken and couriered to a laboratory for double checking. According to the test results, the GP would call the patient to discuss the results and determine whether any dose adjustment is required. As a result, the difference in cost to NHS between warfarin and LMWH is narrower in the community once the extra costs from staff, transportation to visit the patients and repeat tests are added to the cost of the drugs.
Quality of evidence	One concern in the evidence comparing LMWH or VKA was the variation in doses used in studies. Some studies used therapeutic doses for both LMWH and VKA, while others compared prophylactic doses of LMWH to therapeutic doses of VKA. The regimen followed when starting treatment was also not always clearly defined, and INR targets in older studies may be different from current normal ranges. Therefore, the evidence needs to be interpreted with caution, particularly for bleeding rates and VTE recurrences (which are also often poorly defined in the studies). For the most appropriate maintenance treatment duration, low quality evidence suggests that 6 months of oral VKA has no benefit over 3 months for the continuation phase of anticoagulant therapy for patients with PE or DVT. There were only two studies: one study recruited about 40 patients with first DVT and unknown risk factor. The second study recruited 810 patients with DVT or PE without persistent risk factors (provoked). Although there were limitations, this study, which was conducted in the UK, suggested that 6 months of VKA do not offer additional benefits in preventing recurrent VTE (most events happen after stopping VKA), but there may be an important increase in the risk of major bleeding. No economic evidence was found that compared treatment for 3 months with treatment for 6 months.
Other considerations	The emphasis of this recommendation is providing adequate anticoagulation using VKAs to patients with proximal DVT or PE. The minimum duration recommended for all patients with proximal DVT or PE, but without active cancer is 3 months. The additional benefits of extending treatment beyond 3 months are less clear and need to be considered for each patient based on their risk of recurrences and bleeding. Patient preference and the likelihood of patient adherence with the treatment and the monitoring of INR are also important considerations in deciding the most appropriate treatment duration and choice of agents. In the absence of obvious clinical benefits from using LMWH in patients without cancer, and uncertainty about the best dosage, VKA remains the agent of choice for maintenance treatment. Moreover, VKAs can be taken orally while LMWH have to be injected subcutaneously and are more expensive. This is an important practical consideration, since patients have to use it for at least 3 months.

Recommendations	**17. Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment (see recommendations 18**Error! Reference source not found. **and 19).**
	The GDG took into account that it is current standard practice to anticoagulate patients with VKA for three or six months following a first episode of VTE. There is widespread acceptance that three months is an adequate duration of treatment for provoked VTE, and resources are already in place for this recommendation. The GDG recognised that this recommendation requires a risk assessment to decide whether to continue treatment beyond 3 months, and this may have clinical, resource and/or economic implications to the NHS. However, this risk assessment is necessary, because the balance of risk and benefit for continuing treatment is not straightforward. The decision will often be taken in a secondary care setting. This is discussed in further detail in (the following) recommendations for patients with unprovoked proximal DVT or PE (recommendations 18-19). Patients who do not adhere to follow up visits and INR monitoring such as some intravenous drug abusers may be at higher risk of poor anticoagulation control, bleeding and VTE recurrences. This needs to be assessed when deciding treatment choices. VKA use also needs to be considered in groups prone to falls, such as the elderly, as they will be at an increased risk of bleeds. In patients where VKA cannot be adequately monitored, alternative treatments may be required.

Recommendations	**18. Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.**
Relative values of different outcomes	Recurrent VTE and major bleeding (such as fatal bleeding and intracranial bleeding) were considered the most important outcomes. All cause mortality, VTE related mortality, quality of life, and PTS were also considered to be important.
Trade off between clinical benefits and harms	The balance between a decrease in recurrent VTE and increased risk of major bleeding and the associated morbidity and mortality was the main clinical trade off in this recommendation. An economic model was conducted to incorporate the trade off between the benefits and harms (see economic considerations below). The model found that long-term VKA treatment beyond the first 3 months is cost-effective in patients with unprovoked PE unless the risk of major bleeding is increased. Long-term VKA treatment is likely to be beneficial for the majority of patients with an unprovoked PE. Therefore it should be offered to all patients with unprovoked PE unless an increased risk of major bleeding is not balanced by an increased risk of VTE recurrence. For example, patients with twice the baseline risk of bleeding will still have an overall benefit from treatment if the risk of VTE recurrence is also twice the baseline. However, they will have more potential harm than benefit if they do not have risk factors that put them at an increased risk of VTE recurrence. Therefore individual risk factors need to be considered carefully to ensure the balance between VTE recurrence and major bleeding is taken into account.
Economic considerations	An original economic model was conducted. In the base case analysis where the risk of VTE recurrence was 8.4% in patients with an initial proximal DVT and 7.4% in patients with an initial PE the proportion of recurrences as PE was higher in the PE group (50%) compared to the proximal DVT group (15%). Given the high burden of PE episodes in terms of costs and increased mortality, in the base case analysis extending treatment beyond three months is cost-effective in patients after an initial idiopathic PE episode but it is not cost-effective in patients after an initial proximal DVT episode. We conducted a two-way sensitivity analysis and a threshold analysis to analyse the impact of the risk of major bleeding and VTE recurrence on the final results. Long-term treatment is always cost-effective in patients with PE unless the risk of major bleeding is increased. For example, long-term treatment is cost-effective for patients in whom the risk of major bleeding is twice the baseline only if the risk of VTE recurrence is also at least twice the baseline. However, it is not cost-effective if patients do not have risk factors that put them at an increased risk of VTE recurrence.
Quality of evidence	Moderate to low quality evidence suggests that long-term anticoagulant treatment benefits patients with unprovoked PE. There was some concern over heterogeneous populations in the studies and differing lengths of treatment and follow up. The economic evidence had some potentially serious limitations and partial applicability. The model was based on limited clinical evidence (only one RCT for the estimate of effectiveness) and there was some heterogeneity in the population of the studies informing different parameters. In addition, the model required a lifetime extrapolation on short-term data. Some parameters (for example risk of major bleeding while on treatment) were obtained from a slightly different population (patients treated with anticoagulants for non-rheumatic atrial fibrillation).

Recommendations	**18. Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.**
Other considerations	VKA anticoagulation only offers prevention while on treatment and therefore may have to be extended as long as the underlying risk factor(s) remain(s). Correctly identifying "unprovoked" PE and where there may be permanent underlying risk factors as opposed to "provoked" PE where the risk factors are likely to be temporary(for example, surgery, immobilisation) is the first step. The following are main considerations for recommending offering extending VKA anticoagulation to patients with unprovoked PE beyond three months: • The economic model showed that it is cost effective for most patients with unprovoked PE, unless there are factors which increase their risk of bleeding • PE patients, if they have a VTE recurrence, have a higher chance of getting another PE compared to patients who presented with DVT [15]; hence mortality and morbidity from a VTE recurrence is higher in these patients. Therefore patients with PE are likely to benefit more from VKA treatment compared to patients who had a proximal DVT. The GDG recognised that identifying which patients should have extended VKA treatment beyond 3 months is a pertinent clinical issue. The key factors (VTE recurrence and major bleeding) are different for each patient. Although the economic modelling provided useful data about the risks thresholds for VTE recurrence and major bleeding in order for long-term anticoagulation to be cost effective (see appendix I), there are no simple rules of thumb or validated tools to reliably predict these risks. Thorough risk assessment may have clinical, resource and/or economic implications to the NHS, and the decision will often have to be taken in a secondary care setting. However, this is necessary because the decisions are not straightforward. This recommendation also emphasised discussing with the patient the risks and benefits when deciding whether a patient should continue on VKA as patient preferences are important considerations. In addition, the risk of thrombosis and bleeding may change over time; a review and discussion with a healthcare professional is required annually or when there is a change of circumstances affecting these risks. Clinical evidence from RCTs is only available for up to 2-3 years of follow up and longer term data is required (a research recommendation has been made in this guideline see section 7.6) to identify groups for indefinite anticoagulation. The likelihood of patient adherence with the treatment and monitoring of INR are also important considerations. Those with poor adherence may be at higher risk of poor anticoagulation control, bleeding and VTE recurrences. Groups at risk of poor adherence and/or poor INR control include patients with mental health or cognitive problems and IV drug abusers. For cancer patients who have completed the minimum 6 months duration of LMWH recommended, the option of long-term anticoagulation should be discussed. Whether this long-term treatment is with LMWH or VKA is unclear and will depend on individual circumstances.

Recommendations	**19. Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.**
Relative values of different outcomes	Recurrent VTE and major bleeding (such as fatal bleeding and intracranial bleeding) were considered the most important outcomes. All cause mortality, VTE related mortality, quality of life and PTS were also considered to be important.
Trade off between clinical benefits and harms	The balance between a decrease in recurrent VTE and occurrence of major bleeding was considered. An economic model was conducted to incorporate the trade off between the benefits and harms (see economic considerations below). The model found that long-term treatment is not cost-effective in patients with unprovoked proximal DVT unless the risk of VTE recurrence is increased. In patients with an initial presentation of unprovoked proximal DVT, long-term treatment is likely to be beneficial only for patients with an increased risk of VTE recurrence and with no increased risk of major bleeding. Therefore VKA anticoagulation should be considered for patients with unprovoked proximal DVT only if they have an increased risk of VTE recurrence and no increased risk of major bleeding. For example, patients with twice the baseline risk of VTE recurrence will have an overall benefit from continuing treatment if there is no increase in risk of major bleeding. However they will have more potential harm than benefit if they have risk factors that put them at an increased risk of major bleeding. The individual risk factors need to be considered carefully; the risk of bleeding has to be assessed because any increase in risk of bleeding is likely to outweigh any benefits from extended treatment, even in the presence of risk factors for VTE recurrence.
Economic considerations	An original economic model was conducted. In the base case analysis where the risk of VTE recurrence was 8.4% in patients with an initial proximal DVT and 7.4% in patients with an initial PE; however, the proportion of recurrences as PE was higher in the PE group (50%) compared to the proximal DVT group (15%). Given the high burden of PE episodes in terms of costs and increased mortality, in the base case analysis extending treatment beyond three months is cost-effective in patients after an initial idiopathic PE episode but it is not cost-effective in patients after an initial proximal DVT episode. We conducted a two-way sensitivity analysis and a threshold analysis to analyse the impact of the risk of major bleeding and VTE recurrence on the final results. In patients with proximal DVT long-term treatment becomes cost-effective when there is an increased risk of VTE recurrence and no increased risk of major bleeding. For example, in patients with twice the baseline risk of VTE recurrence, long-term treatment is cost-effective if there is no increase in risk of major bleeding. However, it is not cost-effective if patients have risk factors that put them at an increased risk of major bleeding.
Quality of evidence	Moderate to low quality evidence suggests that long-term anticoagulant treatment may benefit some groups of patients with unprovoked proximal DVT. There was concern over heterogeneous populations in the studies and the differing length of treatment and follow up. The economic evidence had some potentially serious limitations and partial applicability. The model was based on limited clinical evidence (only one RCT for the estimate of effectiveness) and there could be some heterogeneity in the population of the studies informing different parameters. In addition, the model required a lifetime extrapolation on short-term data. Some parameters (for example risk of major bleeding while on treatment) were obtained from a slightly different population (patients treated with anticoagulants for non rheumatic atrial fibrillation).

Recommendations	**19. Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment.**
Other considerations	VKA anticoagulation only offers prevention while on treatment and therefore this may have to be extended as long as the underlying risk factor(s) remain(s). Correctly identifying "unprovoked" proximal DVT and where there may be permanent underlying risk factors as opposed to "provoked" proximal DVT where the risk factors are more likely to be temporary (for example, surgery, immobilisation) is the first step. The following are the main reasons for a more cautious recommendation of "considering" long-term VKA treatment for patients who had unprovoked proximal DVT: • The economic model showed that it is not cost effective, unless a patient has factors which further increase the risk of recurrence. The GDG discussed that men with unprovoked VTE have been reported to have higher risk of VTE recurrence.[56,158,206] The other potential factors include PTS[206,232] and a raised D-dimer after stopping anticoagulation.[182,255] • The risk of recurrence as PE is lower in these patients, and therefore there is potentially less morbidity and recurrence is less likely to be life-threatening than in patients with PE (who have proportionately more recurrences as PE). The GDG recognised that identifying which patients should have extended VKA treatment beyond 3 months is a pertinent clinical issue. Conducting a risk assessment may have clinical, resource and/or economic implications to the NHS and the decision will often be taken in a secondary care setting. However, this is necessary because there are no valid and reliable tools to accurately predict risk of bleeding or VTE recurrence. This recommendation emphasised discussion with the patient because the risk benefit is very patient specific and patient preferences are particularly important here. Unlike patients who presented with unprovoked PE, long-term VKA anticoagulation beyond 3 months will only be cost effective to patients who have above average risk of recurrence (compared to other unprovoked DVT/VTE patients), and do not have risk factors (apart from VKA treatment) which put them at higher risk of bleeding. The risk of thrombosis and bleeding may change over time and it is important to have a review annually and if circumstances change for patients who are continuing on treatment. The likelihood of patient adherence to the treatment and the monitoring of INR to maintain good anticoagulation control are also important considerations. Groups at risk of poor adherence and/or poor INR control include patients with mental health or cognitive problems and IV drug abusers. The GDG have prioritised this recommendation as a key priority for implementation as they considered that it has a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes patient choice, promotes equalities and means patients reach critical points in the care pathway more quickly.

7.6 Summary of research recommendations

1. **What is the clinical and cost effectiveness of long-term oral anticoagulation treatment in specific subgroups of patients with first unprovoked VTE?**

There is evidence that some risk factors, such as male sex, raised D-dimer or the presence of post-thrombotic syndrome, are associated with a greater risk of VTE recurrence than others. Although it is thought that subgroups with these risk factors are at increased risk of VTE recurrence, high-quality evidence on the benefits of extending anticoagulation treatment in these subgroups is lacking. An RCT comparing extended long-term oral anticoagulation with 3 months of oral anticoagulation treatment in patients with first unprovoked VTE is needed to determine the relative benefits and risks of long-term oral anticoagulation treatment in these subgroups. The trial should include initial presentation because, compared with a DVT, a PE is a stronger predictor of a future PE, and therefore initial presentation is likely to be a factor in the decision to offer long-term oral anticoagulation. The trial should include the following outcomes: all-cause mortality, VTE recurrence, major bleeding and quality of life. Follow-up should be for 5 years. The results would inform the recommendation in this guideline on continuing oral anticoagulation treatment beyond 3 months.

2. **In patients with VTE and active cancer who have had 6 months of anticoagulation treatment with LMWH, what is the clinical benefit (in terms of VTE recurrence rates, all-cause mortality and major bleeding) and cost effectiveness of continued anticoagulation treatment with LMWH versus a VKA?**

Determining whether LMWH or a VKA should be used for anticoagulation treatment in patients with cancer beyond the initial 6 months of LMWH therapy is critically important. The current recommendation for use of LMWH for the initial 6 months is based on a systematic review that showed LMWH to be advantageous compared with VKA; however, evidence was available only up to 6 months of anticoagulation with VKA. The relative benefits of LMWH or a VKA beyond the initial 6 months are therefore unknown. An RCT is urgently needed to answer this question. The trial should recruit patients with VTE associated with cancer who have completed 6 months of LMWH treatment, in whom long-term treatment is planned, and who have no contraindication to further anticoagulation treatment with either LMWH or a VKA. Patients should be randomised to treatment with either LMWH or a VKA. The primary outcome measure should be VTE recurrence rates. Secondary outcomes should include cost effectiveness and quality of life. Such a trial will provide an evidence-based understanding of the relative benefits and risks of long-term treatment with LMWH versus long-term treatment with a VKA, inform patient and clinician choice, enable development of clear guidelines to minimise variability in care and make the best use of NHS resources.

8 Thrombolytic therapy for DVT

8.1 Introduction

The use of thrombolytic agents such as streptokinase, urokinase and recombinant tissue-type plasminogen activator (r-tPA) in the treatment of deep vein thrombosis (DVT) aims to bring about clot lysis (breakdown of the clot) and rapid normalisation of venous blood flow. These agents can be given via 'catheter directed' (referred to as 'catheter or vein directed' in the evidence of this chapter) administration or 'systemic' administration. 'Catheter directed' administration involves the infusion of the drug by a catheter inserted directly into the affected veins whereas 'systemic' administration involves administration of the drug into an unaffected peripheral vein which then allows the drug to be carried in the circulation to the affected veins.

Recent practice has moved towards using 'catheter directed' administration rather than 'systemic' administration because it is thought to be a more targeted approach which maybe associated with fewer bleeding complications. For this clinical question we consider and compare the clinical effectiveness of DVT thrombolytic therapy for both 'catheter directed' and 'systemic' administration.

DVT thrombolysis has the potential of reducing the risk of PE as well as lowering the incidence of post thrombotic syndrome (PTS). Although anticoagulation treatment is probably as effective if started promptly and at the correct dose for many DVTs, it is unclear whether patients presenting with symptomatic ilio-femoral clots will further benefit with treatment with thrombolytics to reduce PTS. There may, however be an increased risk of major bleeding with thrombolysis.

Mechanical thrombectomy is sometimes combined with thrombolysis and additionally involves mechanical agitation or disruption of the thrombus. Similarly, the thrombus can also be removed with suction catheters in combination with thrombolytic agents. Occasionally direct surgical removal of the thrombus is performed when there is no time for thrombolysis and the limb is threatened.

In this chapter, the risk-benefit of thrombolytic therapy for patients with DVT is considered by looking at patient important outcomes, such as mortality, risk of bleeding, recurrence of VTE and PTS.

8.1.1 What is the effectiveness of thrombolytic therapy and mechanical thrombectomy to manage acute DVT?

See clinical evidence tables in Appendix E.9. and forest plots in Appendix G.4.

8.1.1.1 Clinical evidence

One Cochrane review[259] was identified that included 12 randomised controlled trials. Four studies were catheter or vein directed and six studies used systemic thrombolysis. One study had catheter or vein directed thrombolysis and systemic thrombolysis interventions [221] Two additional studies which were not included in the Cochrane review were found and included.[221,222]

In each study, thrombolysis treatment was compared to a standard anticoagulation regime, for example, heparin alone. The details of each control group can be found in appendix E.9.

No randomised control trials were identified comparing mechanical thrombectomy with either standardised heparin regimes or traditional thrombolysis.

Table 55: Thrombolytic therapy vs standard anticoagulation – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
All cause mortality 6,39,64,115,123,216,221,222	7	RCT	Serious [a, c, d]	No serious inconsistency	No serious indirectness	Serious [b]
Subgroup: vein or catheter directed 64,123,221,222	*4*	*RCT*	*Serious [a, c, d]*	*No serious inconsistency*	*No serious indirectness*	*Serious [b]*
Subgroup: Systemic 6,39,115,216,221	*5*	*RCT*	*Serious [a, c, d]*	*No serious inconsistency*	*No serious indirectness*	*Serious* [b]
VTE related mortality 6,115,123,221,222	5	RCT	Serious [a, d]	No serious inconsistency	No serious indirectness	Serious [b]
Subgroup: vein or catheter directed 221,222	*2*	*RCT*	*Serious* [a, d]	*No serious inconsistency*	*No serious indirectness*	*Serious* [b]
Subgroup: Systemic 6,115,123	*4*	*RCT*	*Serious* [a, d]	*No serious inconsistency*	*No serious indirectness*	*Very serious* [b]
Major Bleeding 6,39,64,80,115,123,216,220-222,246,254	12	RCT	*Serious [a, c, d]*	Serious inconsistency [e]	No serious indirectness	*Serious* [b]
Subgroup: vein or catheter directed, 64,80,123,220-222	*6*	*RCT*	*Serious [a, c, d]*	*No serious inconsistency*	*No serious indirectness*	*Serious* [b]
Subgroup: Systemic 6,39,115,216,221,246,254	*7*	*RCT*	*Serious [a, c, d]*	*No serious inconsistency*	*No serious indirectness*	*No serious imprecision*
Recurrent VTE 6,39,64,221,222	5	RCT	*Serious* [a,(d)]	Serious [e]	No serious indirectness	Serious [b]
Subgroup: vein or catheter directed 64,221,222	*3*	*RCT*	*Serious [a, c, d]*	*No serious inconsistency*	*No serious indirectness*	*No serious imprecision*
Subgroup: Systemic 6,39,221	*3*	*RCT*	*Serious* [a, d]	*No serious inconsistency*	*No serious indirectness*	*Very serious [b]*
Quality of life	0	-	-	-	-	-
Length of hospital stay 222	1	RCT	Serious [c, d]	No serious inconsistency	No serious indirectness	No serious imprecision
Post thrombotic syndrome 6,220,222	3	RCT	Serious [a, d]	Serious [e]	No serious indirectness	No serious imprecision
Subgroup: vein or catheter directed 220,222	*2*	*RCT*	*Serious* [a, d]	*No serious inconsistency*	*No serious indirectness*	*Serious* [b]
Subgroup: Systemic 6	*1*	*RCT*	*No serious limitations*	*No serious inconsistency*	*No serious indirectness*	*Very serious imprecision* [b]
Heparin induced thrombocytopenia	0	-	-	-	-	-

(a) Over 50% of the studies included had unclear descriptions of randomisation.

(b) The CI crosses one or both MID thresholds making the effect size uncertain.
(c) There was unclear blinding in one study.[222]
(d) Unclear allocation concealment in over 50% of the included studies.
(e) There was heterogeneity between subgroups.

Table 56: Thrombolytic therapy vs standard anticoagulation – Clinical summary of findings

Outcome	Thrombolytic therapy	Standard anticoagulation	Relative Risk	Absolute effect	Quality
All cause mortality	8/391 (2%)	10/244 (4.1%)	RR 0.83 (0.37 to 1.9)	7 fewer per 1000 (from 26 fewer to 37 more)	LOW
Subgroup: vein or catheter directed	*3/220 (1.4%)*	*7/143 (4.9%)*	*RR 0.46 (0.13 to 1.57)*	*26 fewer per 1000 (from 43 fewer to 28 more)*	*LOW*
Subgroup: Systemic	*5/171 (2.9%)*	*3/101 (3%)*	*RR 1.57 (0.47 to 5.19)*	*17 more per 1000 (from 16 fewer to 126 more)*	*LOW*
VTE related mortality	1/333 (0.3%)	5/182 (2.7%)	RR 0.27 (0.05 to 1.62)	20 fewer per 1000 (from 26 fewer to 17 more)	*LOW*
Subgroup: vein or catheter directed	*1/191 (0.5%)*	*4/117 (3.4%)*	*RR 0.25 (0.03 to 2.22)*	*26 fewer per 1000 (from 33 fewer to 41 more)*	*LOW*
Subgroup: Systemic	*0/142 (0%)*	*1/65 (1.5%)*	*RR 0.33 (0.02 to 7.32)*	*10 fewer per 1000 (from 15 fewer to 95 more)*	*VERY LOW*
Major Bleeding	53/545 (9.7%)	19/328 (5.8%)	RR 1.9 (1.17 to 3.08)	52 more per 1000 (from 10 more to 121 more)	LOW
Subgroup: vein or catheter directed	*13/319 (4.1%)*	*5/178 (2.8%)*	*RR 1.28 (0.52 to 3.12)*	*8 more per 1000 (from 13 fewer to 59 more)*	*LOW*
Subgroup: Systemic	*40/226 (17.7%)*	*14/150 (9.3%)*	*RR 2.22 (1.25 to 3.96)*	*113 more per 1000 (from 23 more to 275 more)*	*MODERATE*
Recurrent VTE	12/345 (3.5%)	13/192 (6.8%)	RR 0.53 (0.22 to 1.29)	32 fewer per 1000 (from 53 fewer to 20 more)	VERY LOW
Subgroup: vein or catheter directed	*2/209 (1%)*	*13/134 (9.7%)*	*RR 0.19 (0.05 to 0.7)*	*79 fewer per 1000 (from 29 fewer to 92 fewer)*	*MODERATE*
Subgroup: Systemic	*10/136 (7.4%)*	*0/58 (0%)*	*RR 4.16 (0.49 to 35.24)*	*Not estimable*	*VERY LOW*
Length of hospital stay [mean, (SD)]	2.7 (1.1) n=91	5.8 (1.3) n=92	-	MD -3.1 (-3.45 to -2.75)	MODERATE
Post thrombotic syndrome	33/65 (50.8%)	32/44 (72.7%)	RR 0.64 (0.47 to 0.88)	262 fewer per 1000 (from 87 fewer to 385 fewer)	LOW
Subgroup: vein or catheter directed	*28/44 (63.6%)*	*18/23 (78.3%)*	*RR 0.81 (0.6 to 1.11)*	*149 fewer per 1000 (from 313 fewer to 86 more)*	*LOW*
Subgroup: Systemic	*5/21 (23.8%)*	*14/21 (66.7%)*	*RR 0.36 (0.16 to 0.81)*	*427 fewer per 1000 (from 127 fewer to 560 fewer)*	*LOW*

8.1.1.2 Economic evidence

No studies were included for this question. Two studies[125,143] were excluded as they were not applicable because they reported only the hospital or material cost from the perspective of a hospital in the USA. In addition, in both studies, catheter-directed thrombolysis was compared to catheter-directed thrombolysis with mechanical thrombectomy rather than being compared to standard anticoagulation treatment.

The costs to be considered when comparing thrombolytic treatment with standard anticoagulation are:

- Materials and equipment
- Length of hospital stay
- Treating further events: major bleeding and post-thrombotic syndrome.

Based on the results of the clinical review, thrombolytic therapy is likely to increase initial costs of material and length of stay, and the cost of treating major bleeding. However it is likely to decrease the cost of treating post-thrombotic syndrome.

8.1.1.3 Evidence statements

Clinical

All cause mortality

Seven studies with 635 people showed that it is uncertain whether there is a clinically important difference in all cause mortality between thrombolytic therapy and standard pharmacological therapy or placebo (LOW QUALITY).

Four studies with 363 people showed that it is very uncertain whether there is a clinically important difference in all cause mortality between vein or catheter directed thrombolytic therapy and standard pharmacological therapy or placebo (LOW QUALITY).

Five studies with 272 people showed that it is very uncertain whether there is a clinically important difference in all cause mortality between systemic thrombolytic therapy and standard pharmacological therapy or placebo (LOW QUALITY).

VTE related mortality

Five studies with 515 people showed that it is very uncertain whether there is a clinically important difference in VTE related mortality between thrombolytic therapy and standard pharmacological therapy or placebo (LOW QUALITY).

Two studies with 308 people showed that it is very uncertain whether there is a clinically important difference in VTE related mortality between vein or catheter directed thrombolytic therapy and standard pharmacological therapy or placebo (LOW QUALITY).

Four studies with 207 people showed that it is very uncertain whether there is a clinically important difference in VTE related mortality between systemic thrombolytic therapy and standard pharmacological therapy or placebo (VERY LOW QUALITY).

Major bleeding

Twelve studies with 873 people showed that it is very uncertain whether there is a clinically important difference in major bleeding between thrombolytic therapy and standard pharmacological therapy or placebo (LOW QUALITY).

Six studies with 497 people showed that it is very uncertain whether there is a clinically important difference in major bleeding between vein or catheter directed thrombolytic therapy and standard pharmacological therapy or placebo (LOW QUALITY).

Seven studies with 376 people showed that it is very uncertain whether there is a clinically important difference in major bleeding between systemic thrombolytic therapy and standard pharmacological therapy or placebo (MODERATE QUALITY).

Recurrent VTE

Five studies with 537 people showed that it is very uncertain whether there is a clinically important difference in recurrent VTE between thrombolytic therapy and standard pharmacological therapy or placebo (VERY LOW QUALITY).

Three studies with 343 people showed that there were clinically important fewer incidences of recurrent VTE in the vein or catheter directed thrombolytic therapy group than in the standard pharmacological therapy or placebo group (MODERATE QUALITY).

Three studies with 194 people showed that it is very uncertain whether there is a clinically important difference in recurrent VTE between systemic thrombolytic therapy and standard pharmacological therapy or placebo (VERY LOW QUALITY).

Length of hospital stay

One study with 183 people showed that there was a clinically important reduction in length of hospital stay in the thrombolytic therapy group compared to the standard pharmacological therapy or placebo group [The included study used vein or catheter directed thrombolytic therapy] (MODERATE QUALITY).

PTS

Three studies with 109 people showed that there are fewer instances of PTS in the thrombolytic therapy group compared to the standard pharmacological therapy or placebo group, but the difference is not clinically important (LOW QUALITY).

Two studies with 67 people showed that it is unlikely that there is any difference of clinical importance in occurrence of PTS between vein or catheter directed thrombolytic therapy group and the standard pharmacological therapy or placebo group (LOW QUALITY).

One study with 42 people showed that there are fewer instances of PTS in the systemic thrombolytic therapy group compared to the standard pharmacological therapy or placebo group, but the difference is not clinically important (LOW QUALITY).

Economic — No economic evidence was included.

8.2 Recommendations and link to evidence

Recommendations	**20. Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have:** • **symptoms of less than 14 days' duration *and*** • **good functional status *and*** • **a life expectancy of 1 year or more *and*** • **a low risk of bleeding.**
Relative values of different outcomes	The incidence of PTS and bleeding were considered the most important outcomes. All cause mortality is also an overall safety indicator of the treatment.
Trade off between clinical benefits and harms	The balance between increased bleeding was considered against a lower incidence of PTS. The evidence stated that there was an important reduction in the incidence of PTS when thrombolytic therapy was used, compared to just anticoagulation with heparin. Catheter directed thrombolysis may be safer than systemic thrombolysis. Although the risk of major bleeding increased, this is less apparent for catheter directed thrombolysis compared to systemic thrombolysis. In addition, it was observed that there may be fewer deaths from catheter directed thrombolysis compared to systemic thrombolysis. On balance, catheter directed thrombolytic therapy may be considered as an option for a suitable patient, because of the important decrease in PTS from using this therapy. However, the risk of bleeding will make this inappropriate in patients with a pre-existing increased risk of bleeding.
Economic considerations	Based on the results of the clinical review, thrombolytic therapy is likely to increase initial costs of material and length of stay, and the cost of treating major bleeding. However, it is likely to decrease the cost of treating PTS. Selecting the patients that can benefit the most from this treatment improves outcomes (e.g. minimises episodes of major bleeding) making the intervention more cost-effective.
Quality of evidence	There was moderate to very low quality evidence available for all outcomes. There was no evidence found for quality of life or for heparin induced thrombocytopaenia (HIT). We considered different modes of delivery of thrombolytics by analysing catheter or vein directed compared to systemic approach. The following six studies: Elsharawy 2002, Goldhaber 1990, Kill 1981, Schweizer 1998, Schweizer 2000 and Tsapogas 1973 were all catheter/vein directed.[64,80,123,220,221,245] Although there was no statistical heterogeneity observed for most outcomes, it was observed from the forest plots that catheter directed thrombolytic therapy had lower relative risks of harms than the systemic thrombolysis, especially for the outcomes of major bleeding and recurrent VTE. There was only one study that reported an outcome for length of hospital stay,[222] this study looked at catheter or vein directed thrombolysis. There was an overall reduction in PTS in those people who received thrombolysis; however this may be due to the large effect size from one study[6]

Recommendations	**20. Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have:** • **symptoms of less than 14 days' duration *and*** • **good functional status *and*** • **a life expectancy of 1 year or more *and*** • **a low risk of bleeding.**
	of systemic thrombolytic therapy as the decrease in PTS was smaller in catheter or vein directed thrombolytic therapy. There were important limitations in the evidence reviewed. The duration of follow up was available for only up to 6 months. The main benefit of treatment from thrombolysis is likely to be the reduction of PTS, and this benefit is not likely to be apparent in a short follow up of only up to 6 months. Longer follow up will be required to fully characterise this. No economic evidence was included on this question.
Other considerations	In practice relatively few catheter directed thrombolysis interventions are undertaken in the NHS. Catheter directed thrombolysis could potentially bring important benefits to patients. Selecting the patients that can benefit the most from this treatment which makes the intervention have a favourable risk-benefit ratio, is key. The key aspects to consider when deciding whether treatment is suitable are: • The patient's risk of bleeding - as there is an increased risk of bleeding from this intervention, patients with a pre-existing increased risk of bleeding should not be considered for thrombolytic therapy. Patients who have recent trauma or an operation which puts them at an increased risk of bleeding may not be suitable for thrombolysis. A full medical history is required, and this should be documented. • The patient's present symptoms are for less than 14 days – as a thrombus becomes "older" it is less likely to be dissolved by thrombolytic therapy. Additionally the venous valves are more likely to be damaged and less likely to recover their function. This means that thrombolysis may not be as effective after 14 days. • Good functional status – this is important because a patient with good functional status will generally have more rapid clearance of the thrombus and the potential to preserve valvular function. This can potentially lead to a better outcome from thrombolytic therapy, including less swollen legs and a quicker return to normal daily activities. • Life expectancy more than one year – the main benefit of this treatment is the reduction of PTS, which may develop over years and have significant long term impact on the patient's quality of life. If the life expectancy of the patient is short, the risk taken (for major bleeding) may not be worth the benefit expected from PTS reduction. The risks vs benefits of performing this treatment need to be discussed with patients, and their choices taken into account. PTS is a long term problem with significant impact on patients' quality of life, and NHS resources to provide management for this chronic problem. Any interventions which reduce this condition are important for both patients and the NHS. Special groups to consider: drug abusers, peri-partum, post trauma or major abdominal surgery and past history of haemorrhagic stroke. These groups have

Recommendations	**20. Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have:** • **symptoms of less than 14 days' duration *and*** • **good functional status *and*** • **a life expectancy of 1 year or more *and*** • **a low risk of bleeding.**
	a higher risk of haemorrhagic complications. The GDG have prioritised this recommendation as a key priority for implementation. They considered it to have a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes patient choice, promotes equalities and means patients reach critical points in the care pathway more quickly. The GDG discussed that there may be some resource implications for centres which do not currently offer this treatment and that change to facilities or local referral arrangements might have to be made for appropriate patients. Improvement to the availability of this treatment was considered important when the GDG discussed and voted for the key priorities for implementation. Recommendations for anticoagulation treatment for patients with confirmed DVT are detailed in the Pharmacological chapter (Section 7.5 Recommendations and link to evidence).

8.3 Summary of research recommendations

3. What is the clinical and cost effectiveness of clot removal using catheter-directed thrombolytic therapy or pharmacomechanical thrombolysis compared with standard anticoagulation therapy for the treatment of acute proximal DVT?

Clot removal strategies such as catheter-directed thrombolysis might be more effective than standard anticoagulation treatment in reducing post-thrombotic syndrome. However, there is an increased risk of major bleeding with these strategies. Evidence was identified on outcomes (mortality, major bleeding, post thrombotic syndrome and recurrent DVT) related to clot removal strategies for the treatment of acute (less than 14 days' duration) proximal DVT. However, the studies had important methodological limitations and the follow-up periods were only 6 months. It is important to have longer-term (at least 2 years) and higher-quality evidence from RCTs to inform the decision on whether to use clot removal strategies for the treatment of acute proximal DVT. Catheter-directed or pharmacomechanical thrombolysis should be compared with standard anticoagulation therapy (LMWH or fondaparinux). The primary outcome measures should be mortality, major bleeding, VTE recurrence at 3 months, incidence and severity of post-thrombotic syndrome at 2 years (measured by a validated tool) and quality of life.

9 Thrombolytic therapy for PE

9.1 Introduction

The principle behind thrombolytic therapy for PE is to remove the embolic material from the pulmonary arteries by promoting lysis of blood clots. The thrombolytic agent can either be given into a peripheral vein (systemic thrombolysis) or directly into the pulmonary arteries via a catheter (catheter-directed thrombolysis). Thrombolytic therapy has been used in the treatment of PE for over 40 years. It can also be combined with attempts to break up the thrombus by using mechanical devices inserted via a catheter into the major pulmonary arteries or attempting to suck out (aspirate) the clot. These adjunctive procedures when combined with thrombolysis are termed pharmaco-mechanical thrombolysis. An alternative, used less commonly in modern practice is to operate to remove the clots in the pulmonary arteries directly by a surgical procedure, known as open pulmonary embolectomy.

Pharmacological thrombolytics that have been used in the treatment of PE consist of streptokinase, urokinase and rt-PA. These agents are all plasminogen activators that stimulate the fibrinolytic system leading to the lysis of blood clots. They are all given intravenously. The mechanisms of action of these agents differ slightly; rt-PA is a fibrin-specific agent, preferentially activating plasminogen on the clot surface, whilst streptokinase and urokinase are non-selective agents.

Intrapulmonary local infusion of the thrombolytic agent has not been shown to more effective compared to intravenous thrombolysis administered via a peripheral vein (systemic) and it carries an increased risk of bleeding at the puncture site. Hence, in most centres, systemic thrombolysis is used. In specialised centres percutaneous interventional catheterisation techniques have also been utilised (catheter directed thrombolysis). It is unclear whether one of these treatment modalities is better than the other, particularly in terms of risk of major bleeding.

Percutaneous catheter embolectomy and fragmentation:

Percutaneous techniques to open occluded main pulmonary arteries may involve suction embolectomy, thrombus fragmentation using balloon angioplasty, a rotational pigtail catheter or rheolytic therapy where the venturi effect created by a high-speed saline jet fragments the thrombus. Complications include perforation or dissection, pericardial tamponade, pulmonary haemorrhage, distal thrombus embolisation, catheter induced arrthymias, contrast reactions and access site haematoma. Available evidence is limited to case series and the procedure should be terminated as soon as haemodynamics improve, regardless of the angiographic result.

Patients presenting with an acute PE with a prior history of exertional breathlessness may have acute on chronic thromboembolic disease. In those who develop chronic thromboembolic pulmonary hypertension pulmonary endarterectomy surgery in a specialised centre rather than a pulmonary embolectomy is required.

Open surgical pulmonary embolectomy:

In centres with cardiac surgical programmes, open surgical pulmonary embolectomy has been used to restore patency of the pulmonary vasculature in haemodynamically unstable patients particularly where pharmacological thrombolytic therapy is contra-indicated or has failed. The evidence of its benefit remains limited owing to the small number of clinical trials reporting on its effectiveness as well as its overall impact on mortality. Open pulmonary embolectomy is only rarely performed in current practice and is not widely applicable for the NHS.

The review examined evidence looking into whether thrombolytic therapy should be offered to patients with PE or only certain sub-groups of PE patients. Where possible, we planned a subgroup

analysis in order to identify whether one type of thrombolytic therapy is safer and more effective than others, and to identify whether patients with different levels of severity have different risk-benefit balances.

To identify subgroups of patients who are at increased risk of mortality, some risk stratification tools are available. It has been suggested that early (i.e. in-hospital or 30 day) PE mortality is related to haemodynamic compromise and right ventricular dysfunction [81,117]. Other tools for risk stratification include clinical parameters for example age, comorbidity as used in the PE severity index or Geneva risk prediction model, evidence of right ventricular dysfunction by ECG, echocardiography or CTPA, biomarkers such as brain natriuretic peptide, cardiac troponins or heart type fatty acid binding protein, residual DVT, and the D-dimer level. The ideal combination of prognostic tools for PE risk stratification with the appropriate management strategy remains to be determined.

Examination of the literature revealed a wide-range of terminology used to define the severity of PE. For the purposes of this guideline, the most pertinent defining characteristic was chosen to categorise patients/studies into subgroups defined by haemodynamic stability. The two groups identified for which classification was possible were haemodynamically 'unstable' patients and haemodynamically 'stable' patients. The definitions and considerations for these subgroups are discussed below.

Haemodynamically unstable PE - The haemodynamically unstable patient subgroup will include groups previously referred to as massive PE. The haemodynamically unstable patient subgroup can be defined by a systolic blood pressure < 90mmHg or a pressure drop of ≥40 mmHg for >15 minutes if not caused by an arrhythmia, hypovolaemia or sepsis.[244,268] About 5-10% of patients present in this high risk group with a risk of early death of > 15% [9,81,130,147,214,268] and may be initially too unstable to be sent for investigations as recommended in the chapter on PE diagnosis.

Haemodynamically stable PE -The haemodynamically stable patient subgroup will include groups previously referred to as normotensive, non-massive or sub-massive. Within this group there are two subgroups of patients that may be considered separately by clinicians. The first group are considered to be at a lower risk of death and are defined by being haemodynamically stable without evidence of right heart strain and/or myocardial injury. These were previously termed non-massive PE with an early mortality of < 1%.[244] The second group, although still haemodynamically stable, are considered to be at increased risk with an early mortality of 3-15%.[81] These patients are haemodynamically stable with evidence of right heart strain or myocardial injury. This group has been referred to as sub-massive PE.[81] Trials identified have not, to date, classified these groups separately. However, there is an ongoing clinical trial to identify whether thrombolysis will be beneficial for the sub-population of haemodynamically stable PE patients with right ventricular dysfunction (www.clinicaltrials.gov, NCT00639743).

In this chapter we consider the clinical and cost-effectiveness of thrombolytic therapy compared to anticoagulation for people with haemodynamically unstable PE and for people with haemodynamically stable PE. Thrombolytic therapy includes open surgical thrombectomy, mechanical and pharmacological thrombolysis and pharmacological thrombolysis. Clinical trials identified were classified as either of haemodynamically unstable PE or haemodynamically stable PE according to the majority of patients in each group.

9.1.1 What is the effectiveness of open surgical thromboectomy, combination of mechanical and pharmacological thrombolysis, pharmacological thrombolytic therapy and heparin to manage acute PE?

All the studies included compared pharmacological thrombolysis to standard anticoagulation. No suitable mechanical, surgical or percutaneous embolectomy studies were identified for inclusion.

All studies compared pharmacological thrombolytic therapy plus heparin to heparin alone.

See clinical evidence tables in Appendix E.10, forest plots in Appendix G.5 and Economic evidence tables in Appendix F.

9.1.1.1 Clinical evidence

Table 57: Thrombolytic therapy vs heparin for PE – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Imprecision
All cause mortality[1,43,55,67,79,110,129,141,152,234]	10	RCT	Serious limitations[(a)]	No serious inconsistency	No serious indirectness	Serious [(b)]
Subgroup: Unstable[1,55,110,152]	*4*	*RCT*	*Serious limitations[(a)]*	*No serious inconsistency*	*Serious indirectness*[(d)]	*Serious[(b)]*
Subgroup: Stable[43,67,79,129,141,234]	*6*	*RCT*	*Serious limitations[(a)]*	*No serious inconsistency*	*Serious indirectness*[(d)]	*Serious[(b)]*
VTE related mortality[1,43,55,67,79,110,129,141,152,234]	10	RCT	Serious limitations[(a)]	No serious inconsistency	No serious indirectness	Serious[(b)]
Subgroup: Unstable[1,55,110,152]	*4*	*RCT*	*Serious limitations[(a)]*	*No serious inconsistency*	*Serious indirectness*[(d)]	*Serious[(b)]*
Subgroup: Stable[43,67,79,129,141,234]	*6*	*RCT*	*Serious limitations[(a)]*	*No serious inconsistency*	*Serious indirectness*[(d)]	*Serious[(b)]*
Major bleeding[1,43,55,67,79,129,141,152,234]	9	RCT	Serious limitations[(a)]	No serious inconsistency	Very serious indirectness[(d,e)]	Serious[(b)]
Subgroup: Unstable[1,55,152]	*3*	*RCT*	*Serious limitations[(a)]*	*No serious inconsistency*	*Very serious indirectness*[(d,e)]	*Serious[(b)]*
Subgroup: Stable[43,67,79,129,141,234]	*6*	*RCT*	*Serious limitations[(a)]*	*No serious inconsistency*	*Very serious indirectness*[(d,e)]	*Serious[(b)]*
Recurrence of VTE	0[(c)]					
Quality of life	0					
Chronic pulmonary hypertension	0					
Length of hospital stay	0					
Heparin induced thrombocytopenia	0					

a) Seven studies had unclear allocation concealment [1,43,55,129,141,152,234], and eight studies had unclear randomisation method [1,43,55,79,129,141,152,234]. One study had incomplete outcome data that was not addressed [152]. One study was stopped early due to mortality rates [110].Outcomes are downgraded when these studies contributed an important amount of information to the pooled effect size.

b) The CIs crossed one or more MID thresholds.

c) The values for VTE recurrence were not pooled because there was no definition of PE/DVT recurrence in the studies and they did not look specifically for this outcome, probably due to the relatively short length of follow up (usually up to discharge or 30 days, whichever earlier).This outcome is usually reported only whenever a death occurs. Some studies counted any death due to PE as a recurrence, including those that occur within hours, while others do not. Others reported presence of DVT in patients who died for other reasons and counted it as recurrence. Numbers taken from this outcome may have been unreliable and possibly misleading.

d) Severity of PE in patients included into the studies was not classified as "haemodynamically stable" or "haemodynamically unstable" PE. There was a mixture of patients of various severity in many trials. One trial admitted only patients with haemodynamically unstable PE[110], *but this trial was terminated early due to high rates of death in the control arm.*

e) Some studies used only pulmonary angiograms (an invasive procedure) to confirm PE,[1,43,55,152,234] the others used pulmonary angiogram or other non invasive scans[79,129,141,234] while others only used non-invasive techniques.[67,110,141] It is possible this procedure is related to increased number of bleedings observed. A sensitivity analysis conducted showed a higher trend of baseline risks in the trials which used pulmonary angiogram to confirm PE.

Table 58: Thrombolytic therapy vs heparin for PE – Clinical summary of findings

Outcome	Thrombolytic therapy	Heparin	Relative Risk	Absolute effect	Quality
All cause mortality	16/378 (4%)	27/382 (7%)	RR 0.59 (0.34 to 1.04)	29 fewer per 1000 (from 47 fewer to 3 more)	LOW
Subgroup: Unstable	*8/115 (7%)*	*15/109 (14%)*	*RR 0.52 (0.24 to 1.15)*	*66 fewer per 1000 (from 105 fewer to 21 more)*	*VERY LOW*
Subgroup: Stable	*8/263 (3%)*	*12/273 (4%)*	*RR 0.67 (0.3 to 1.51)*	*15 fewer per 1000 (from 31 fewer to 22 more)*	*VERY LOW*
VTE related mortality	6/378 (2%)	17/382 (4%)	RR 0.44 (0.2 to 0.94)	25 fewer per 1000 (from 3 fewer to 36 fewer)	LOW
Subgroup: Unstable	*3/115 (3%)*	*8/109 (7%)*	*RR 0.42 (0.14 to 1.28)*	*43 fewer per 1000 (from 63 fewer to 21 more)*	*VERY LOW*
Subgroup: Stable	*3/263 (1%)*	*9/273 (3%)*	*RR 0.45 (0.16 to 1.28)*	*18 fewer per 1000 (from 28 fewer to 9 more)*	*VERY LOW*
Major bleeding	37/374 (10%)	25/378 (7%)	RR 1.39 (0.87 to 2.23)	26 more per 1000 (from 9 fewer to 81 more)	VERY LOW
Subgroup: Unstable	*27/111 (24%)*	*16/105 (15%)*	*RR 1.58 (0.9 to 2.78)*	*88 more per 1000 (from 15 fewer to 271 more)*	*VERY LOW*
Subgroup: Stable	*10/263 (4%)*	*9/273 (4%)*	*RR 1.06 (0.44 to 2.52)*	*2 more per 1000 (from 18 fewer to 50 more)*	*VERY LOW*

9.1.1.2 Economic evidence

One study[186] was included that compared alteplase plus heparin vs. heparin alone. This is summarised in the economic evidence profile below (Table 58 and Table 59). See also the full study evidence tables in Appendix F. This study was based on the results of one of the RCTs included in our clinical review[129] (see 9.1.1.1).

Table 59: Thrombolytic + standard treatment vs standard treatment - Economic study characteristics

Study	Limitations	Applicability	Other comments
Perlroth 2007[186]	Potentially serious limitations [(a)]	Partially applicable [(b)]	Lifetime Markov model based on a RCT[129] included in our review (see 9.1.1.1). Thrombolytic treatment was with alteplase+heparin while standard treatment was heparin alone. Patients were haemodynamically stable (systolic blood pressure >90 mmHg) with submassive PE and right ventricular dysfunction.

(a) Treatment effects estimated only from one study, unclear how the sources of baseline probabilities have been selected, resources were estimated from clinical trials but these were not explicitly indicated; costs were reimbursement rates.

(b) Analysis conducted from the USA societal perspective, unclear how the sources of quality of life data were selected.

Table 60: Thrombolytic + standard treatment vs standard treatment - Economic summary of findings

Study	Incremental cost per patient (£)	Incremental effects per patient (QALYs)	ICER (£/QALY)	Uncertainty
Perlroth 2007[186]	411 [(a, b)]	-0.051 [(c)]	Standard treatment alone more effective and less costly	Probability cost-effective at a threshold ~£30,000/QALY Standard treatment: 67% Thrombolytic treatment: 33% One-ways SA: at a threshold ~£30,000/QALY thrombolytic treatment becomes cost-effective when RR of death = 0.68 (base case value = 1.0). Results were not sensitive to the other main parameters (risk of treatment escalation, bleeding complications, and cost of alteplase).

(a) 2006 US dollars presented here as 2009 UK pounds, converted using Purchasing Power Parities[177]

(b) Costs incorporated into the model were initial hospitalisation including treatment with heparin or heparin plus altreplase, treatment of recurrent PE, treatment escalation, minor bleeding, severe bleeding, ICH, nursing home care for disability after ICH. Cost of complications was higher for patients responding to primary treatment compared to patients requiring treatment escalation Resource use estimated from trials, costs from Medicare reimbursement rates and other administrative data sources.

(c) Effectiveness (mortality from PE, patients requiring treatment escalation, intracranial haemorrhage) was estimated from an RCT[129] included in our clinical review; risk of bleeding complications was estimated from a multicentre registry and other RCTs. Quality of life data estimated from previous studies.

9.1.1.3Evidence statements

Clinical

Ten studies with 760 patients show there was a decrease which may be of clinical importance in the group treated with thrombolytic therapy compared with heparin alone for all cause mortality (LOW QUALITY).

In the haemodynamically unstable subgroup, four studies with 224 patients show there was a decrease which may be of clinical importance in the group treated with thrombolytic therapy compared with heparin alone for all cause mortality (VERY LOW QUALITY).

In the haemodynamically stable subgroup, six studies with 536 patients show that it is very uncertain whether there is any difference in all cause mortality between the thrombolytic therapy and heparin alone (VERY LOW QUALITY).

Ten studies with 760 patients show there was a decrease which may be of clinical importance in the group treated with thrombolytic therapy compared with heparin alone for VTE related mortality (LOW QUALITY).

In the haemodynamically unstable subgroup, four studies of 224 patients show that it is very uncertain whether there is a clinically important difference in VTE related mortality between thrombolytic therapy and heparin alone (VERY LOW QUALITY).

In the haemodynamically stable subgroup, six studies with 536 patients show that it is very uncertain whether there is any difference in VTE related mortality between the thrombolytic therapy and heparin alone group (VERY LOW QUALITY).

Nine studies with 752 patients show there was an increase which may be of clinical importance in the group treated with thrombolytic therapy compared with heparin alone for major bleeding (VERY LOW QUALITY).

In the haemodynamically unstable subgroup, three studies with 216 patients show there was an increase which may be of clinical importance in the group treated with thrombolytic therapy compared with heparin alone for major bleeding (VERY LOW QUALITY).

In the haemodynamically stable subgroup, six studies with 536 patients show that it is very uncertain whether there is a clinically important difference in major bleeding between thrombolytic therapy and heparin alone (VERY LOW QUALITY).

VTE recurrence has been identified as an important outcome but the data was unreliably reported in the studies.

No studies reported outcomes for quality of life, chronic thromboembolic pulmonary hypertension, length of hospital stay or heparin induced thrombocytopenia.

Economic

Additional pharmacological thrombolytic treatment increases costs and generates fewer QALYs compared to anticoagulation treatment alone in haemodynamically stable (systolic blood pressure >90mmHg) patients with right ventricular dysfunction.

9.2 Recommendations and link to evidence

Recommendations	21. Consider pharmacological systemic thrombolytic therapy for patients with PE and haemodynamic instability (see also recommendation 15).
Relative values of different outcomes	All cause mortality, VTE related mortality and major bleeding were considered the most important outcomes to determine the benefits of the intervention.
Trade off between clinical benefits and harms	The evidence suggests that treatment with pharmacological thrombolytic therapy may have advantages over anticoagulation in the relative reduction of overall mortality and VTE related mortality. However, pharmacological thrombolytic therapy is associated with the increased risk of harm from major bleeding. The overall balance of benefit and harm will be dependent on the baseline risk of death from PE compared against the risk of bleeding. Therefore there is an overall clinical benefit for patients with increased risk of death, but lower risk of bleeding. There is overall harm if the treatment is applied to patients with lower risk of death but higher risk of bleeding. In the evidence reviewed, the baseline risk of mortality i.e. from the heparin alone group in the haemodynamically unstable subgroup is approximately 14% whilst in the haemodynamically stable subgroup it is 4%. Therefore the absolute risk reduction for all cause mortality with thrombolytic therapy is higher in the unstable subgroup (approximately 66 fewer per 1000 patients) than in the stable group (approximately 15 fewer per 1000 patients). The GDG considered pharmacological thrombolytic therapy to have an overall benefit in the haemodynamically unstable subgroup but not the stable subgroup.
Economic considerations	No economic evidence was found on this population. Thrombolytic therapy is likely to increase initial costs of material and length of stay. The overall effectiveness of the interventions is determined by their impact on mortality, the recurrence of PE or DVT, the risk of chronic thromboembolic pulmonary hypertension and the risk of bleeding. As the baseline risks are higher in the haemodynamically unstable population, thrombolytic treatment is likely to be cost-effective for this group.
Quality of evidence	The quality of evidence for all cause mortality, VTE related mortality and major bleeding was very low due to study limitations, indirectness of evidence and very serious imprecision. Various definitions of severity were used for the studies reviewed, and there were no clear differentiation between patients with haemodynamically stable and unstable PE. The values for VTE recurrence were not pooled because most of the studies have a very short time of follow up and were poorly reported. The potential of bias and uncertainty in the clinical evidence led the GDG to make recommendations where treatments should be considered for haemodynamically unstable patients rather than offered. The treatment should be considered by the clinician and patient preference should be taken into account when feasible.
Other considerations	This recommendation was based on the clinical evidence and supported by GDG opinion, and therefore it is a “consider” recommendation. It will be

Recommendations	21. Consider pharmacological systemic thrombolytic therapy for patients with PE and haemodynamic instability (see also recommendation 15).
	important to discuss the options with patients when feasible. The GDG considered the risk of mortality from PE compared to the risk of bleeding as the most important factors in the decision of whether to offer treatment. In haemodynamically unstable patients, there is a higher risk of mortality and the benefit from the reduction of mortality outweighed the risk of bleeding in this group. However within this group there is likely to be heterogeneity and treatment should be considered on a patient to patient basis. The GDG also considered that there are important limitations in the evidence reviewed: • The baseline risk of mortality for the haemodynamically unstable group may be higher, from 15 to 50% based on epidemiological studies and risk registries. • The risk of bleeding in current practice may be lower than in studies; the studies used pulmonary angiography to confirm PE which is invasive and could put the patients at higher risk of bleeding. The evidence available was only for pharmacological therapy and therefore only this has been recommended. Many of the studies were unclear as to whether they had used systemic or catheter-directed pharmacological thrombolytic therapy. As there is a higher risk of bleeding from the puncture site with catheter directed thrombolysis and as it is less widely available, the GDG included the term 'systemic' on consensus. Recommendations for anticoagulation treatment for patients with confirmed PE are detailed in the Pharmacological chapter (Section 7.5 Recommendations and link to evidence)

Recommendation	22. Do not offer pharmacological systemic thrombolytic therapy to patients with PE and haemodynamic stability (see also recommendation 15).
Relative values of different outcomes	All cause mortality, VTE related mortality and major bleeding were considered the most important outcomes to determine the benefits of the intervention.
Trade off between clinical benefits and harms	The evidence suggests that treatment with pharmacological thrombolytic therapy may have advantages over anticoagulation in the relative reduction of overall mortality and VTE related mortality. However, it is also associated with the increased risk of harm from major bleeding. The overall balance of benefit (reduction of mortality) and harm (from bleeding) will be dependent on the baseline risk of death from PE, compared against the risk of bleeding. Therefore, there is an overall clinical benefit for patients with increased risk of death but overall harm if the treatment is applied to patients with a lower risk of death. The baseline risk of mortality i.e. from the heparin alone group in the

Recommendation	22. Do not offer pharmacological systemic thrombolytic therapy to patients with PE and haemodynamic stability (see also recommendation 15).
	haemodynamically unstable subgroup is approximately 14% whilst in the haemodynamically stable subgroup it is 4%. Therefore, the absolute risk reduction for all cause mortality with thrombolytic therapy is higher in the unstable subgroup (approximately 66 fewer per 1000 patients) than in the stable group (approximately 15 fewer per 1000 patients). The GDG considered pharmacological thrombolytic therapy may have an overall benefit in the haemodynamically unstable subgroup but not in the stable subgroup. It was decided there is not enough evidence to justify using this intervention in patients with haemodynamically stable PE, and lower mortality risks.
Economic considerations	One economic study was found where a decision model was developed based on one of the RCTs included in our review; this concluded that adding thrombolytic treatment to standard treatment with heparin alone is not cost-effective. In the base case analysis thrombolytic treatment was more costly and less effective than standard treatment when lifelong consequences were considered and their impact on mortality and quality of life was incorporated in the model.
Quality of evidence	The quality of evidence for all cause mortality, VTE related mortality and major bleeding was very low due to study limitations, indirectness of evidence and very serious imprecision. Various definitions of severity were used for the studies reviewed, and there was no clear differentiation between patients with haemodynamically stable and unstable PE. The values for VTE recurrence were not pooled because most of the studies have a very short time of follow up and were poorly reported. The economic evidence has potentially serious limitations and partial applicability.
Other considerations	This recommendation was based on the consideration of the lack of clinical evidence, and GDG consensus. It is important to discuss the options with patients when feasible. There may be a small reduction in mortality in the haemodynamically stable subgroup but because the baseline risk of mortality is low particularly in those patients without evidence of right heart strain or myocardial injury, further evidence of incremental benefits would be necessary to justify exposing patients to the potential harm of thrombolytic therapy. This is a larger group of patients than the haemodynamically unstable subgroup and this treatment requires close monitoring to be implemented safely. This would require additional resources and would have important cost implications. The GDG discussed that there is potentially a sub-population of haemodynamically stable patients with right ventricular dysfunction for which there is currently an ongoing clinical trial. The GDG recommended that clinicians should consider patients that fit into this category for ongoing clinical trials. Recommendations for anticoagulation treatment for patients with confirmed PE are detailed in the Pharmacological chapter (Section 7.5 Recommendations and link to evidence)

9.3Summary of research recommendations

4. **What is the clinical and cost effectiveness of systemic pharmacological thrombolysis compared with standard initial anticoagulation therapy in patients with confirmed PE and haemodynamic stability who present with right ventricular dysfunction?**

It is unclear from the evidence identified in the review whether there are subgroups of patients with PE and haemodynamic stability who have a significant risk of PE-related mortality and morbidity and would benefit from systemic thrombolysis. No evidence was found in the clinical review for the safety and effectiveness of pharmacological thrombolysis in patients with confirmed PE and haemodynamic stability who present with right ventricular dysfunction. An RCT is needed to compare pharmacological thrombolysis (for example, with alteplase) with standard initial anticoagulation therapy (with LMWH or fondaparinux) in these patients. The important outcomes would be all-cause mortality, VTE-related mortality, cardiopulmonary resuscitation, major bleeding, VTE recurrence and chronic thromboembolic pulmonary hypertension. This research could improve early outcomes and survival, and reduce complications such as chronic thromboembolic pulmonary hypertension, and would inform an update of this guideline. Currently the guideline does not recommend systemic thrombolysis for these patients.

10 Mechanical Interventions

10.1 Introduction

Mechanical interventions refer to the physical (as opposed to pharmacological/chemical) methods of management of patients with DVT. In this chapter we consider the clinical and cost-effectiveness of mechanical interventions compared to pharmacological interventions or no treatment for people with suspected or confirmed DVT. The mechanical interventions considered are vena caval filters and graduated compression hosiery.

10.2 Vena caval filters

Inferior vena caval (IVC) filters were first introduced in 1967 as an alternative to IVC filter ligation. They are designed to trap fragmented thromboemboli from the deep leg veins en route to the pulmonary circulation (whilst preserving blood flow in the IVC filter). Various filters are available and can be placed in the IVC filter on either a temporary or permanent basis. Vena caval filters are most commonly used in patients with a high risk of PE in whom conventional therapy with anticoagulation is contra-indicated or when individuals have had VTE despite anticoagulation. Vena caval filters are usually placed under radiological guidance, approached from either the jugular or femoral vein. They are usually placed infrarenally though not universally so, depending on the clinical situation.

The long term safety of IVC filters is not known and the main complications associated with vena caval filters are filter migration, an increased risk of lower limb DVT caval thrombosis, and rarely, infections. The review was conducted to investigate the clinical and cost effectiveness of vena caval filters to manage VTE in patients who are unable to have pharmacological treatment.

10.2.1 What is the clinical effectiveness of vena caval filters to manage venous thromboemobolic diseases in people that are unable to have pharmacological treatment?

See clinical evidence tables in Appendix E.11 forest plots in Appendix G.6.1.

No RCTs of vena caval filters in patients who were unable to have pharmacological management were found.

Only one study[48] in an indirect population was found, patients included in this study were able to take anticoagulation. This study was a 2x2 factorial design; patients were randomised to vena caval filter or no vena caval filter and LMWH or UFH at the same time and followed up for two years. These two interventions are unlikely to have an interaction, but the evidence was downgraded for indirectness of population.

10.2.1.1 Clinical evidence

Table 61: Vena caval filters vs no vena caval filters – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
All cause mortality						
All cause mortality at 12 days [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Very serious imprecision* (d)
All cause mortality at 2 years [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Very serious imprecision* (d)
All cause mortality at 8 years [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Serious imprecision* (c)
PE						
Symptomatic and asymptomatic at 12 days [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Serious imprecision* (c)
Symptomatic, at 2 years [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Very serious imprecision* (d)
Symptomatic, at 8 years [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Serious imprecision* (c)
Recurrent VTE (symptomatic)						
Recurrent VTE at 2 years [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Serious imprecision* (c)
VTE at 8 years [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Serious imprecision* (c)
Recurrent DVT (symptomatic)						
Recurrent DVT at 2 years [48]	*1*	*RCT*	*Very serious limitations* (a),(b)	*No serious inconsistency*	*Serious indirectness* (e)	*Serious imprecision* (c)
Recurrent DVT at 8 years [48]	*1*	*RCT*	*Very serious limitations* (a),(b)	*No serious inconsistency*	*Serious indirectness* (e)	*Serious imprecision* (c)
Major bleeding						
Major bleeding at 12 days [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Very serious imprecision* (d)
Major bleeding at 2 years [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Very serious imprecision* (d)
Major bleeding at 8 years [48]	*1*	*RCT*	*Very serious limitations* (a, b)	*No serious inconsistency*	*Serious indirectness* (e)	*Very serious imprecision* (d)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Postthrombotic syndrome (at 8 years) [48]	1	RCT	Very serious limitations (a, b)	No serious inconsistency	Serious indirectness(e)	Very serious imprecision(d)

(a) No blinding and unclear allocation concealment. The study used Kaplan-Meier survival analysis to show the cumulative rate of outcomes and used odds ratio or hazard ratio. It was not possible to work out the denominator for each group so our analysis used the number randomised to calculate risk ratio. 372 patients were evaluated at up to two years out of 400 randomised.

(b) 201 patients died by 8 years and data was not available for another 4 patients. Number randomised was used as a denominator in our analysis – number available was not reported for all the outcomes. There was a very important risk of attrition bias for the 8 year data.

(c) CI crossed one MID point.

(d) CI crossed two MID points.

(e) The study compares vena caval filters vs no vena caval filters in patients receiving anticoagulation. This population is different to the population asked in the review question and in the recommendation and was downgraded for indirectness.

Table 62: Vena caval filters vs no vena caval filters - Clinical summary of findings

Outcome	Vena caval filter	No filter	Relative risk (95% CI)	Absolute effect (95% CI)	Quality
All cause mortality					
All cause mortality at 12 days [48]	*5/200 (2.5%)*	*5/200 (2.5%)*	*RR 1 (0.29 to 3.4)*	*0 fewer per 1000 (from 18 fewer to 60 more)*	*VERY LOW*
All cause mortality at 2 years [48]	*43/200 (21.5%)*	*40/200 (20%)*	*RR 1.08 (0.73 to 1.58)*	*16 more per 1000 (from 54 fewer to 116 more)*	*VERY LOW*
All cause mortality at 8 years [48]	*98/200 (49%)*	*103/200 (51.5%)*	*RR 0.95 (0.78 to 1.16)*	*26 fewer per 1000 (from 113 fewer to 82 more)*	*VERY LOW*
PE					
Symptomatic and asymptomatic PE at 12 days [48]	*2/200 (1%)*	*9/200 (4.5%)*	*RR 0.22 (0.05 to 1.02)*	*35 fewer per 1000 (from 43 fewer to 1 more)*	*LOW*
Symptomatic PE, at 2 years [48]	*6/200 (3%)*	*12/200 (6%)*	*RR 0.5 (0.19 to 1.31)*	*30 fewer per 1000 (from 49 fewer to 19 more)*	*VERY LOW*
Symptomatic PE, at 8 years [48]	*9/200 (4.5%)*	*24/200 (12%)*	*RR 0.38 (0.18 to 0.79)*	*74 fewer per 1000 (from 25 fewer to 98 fewer)*	*VERY LOW*
Recurrent VTE (symptomatic)					
Recurrent VTE at 2 years [48]	*37/200 (18.5%)*	*29/200 (14.5%)*	*RR 1.28 (0.82 to 1.99)*	*41 more per 1000 (from 26 fewer to 144 more)*	*VERY LOW*
Recurrent VTE at 8 years [48]	*58/200 (29%)*	*55/200 (27.5%)*	*RR 1.05 (0.77 to 1.44)*	*14 more per 1000 (from 63 fewer to 121 more)*	*VERY LOW*
Recurrent DVT (symptomatic)					
Recurrent DVT at 2 years [48]	*37/200 (18.5%)*	*21/200 (10.5%)*	*RR 1.76 (1.07 to 2.9)*	*80 more per 1000 (from 7 more to 200 more)*	*VERY LOW*

Outcome	Vena caval filter	No filter	Relative risk (95% CI)	Absolute effect (95% CI)	Quality
Recurrent DVT at 8 years [48]	*57/200 (28.5%)*	*41/200 (20.5%)*	*RR 1.39 (0.98 to 1.97)*	*80 more per 1000 (from 4 fewer to 199 more)*	*VERY LOW*
Major bleeding					
Major bleeding at 12 days [48]	*9/200 (4.5%)*	*6/200 (3%)*	*RR 1.5 (0.54 to 4.14)*	*15 more per 1000 (from 14 fewer to 94 more)*	*VERY LOW*
Major bleeding at 2 years [48]	*17/200 (8.5%)*	*22/200 (11%)*	*RR 0.77 (0.42 to 1.41)*	*25 fewer per 1000 (from 64 fewer to 45 more)*	*VERY LOW*
Major bleeding at 8 years [48]	*26/200 (13%)*	*31/200 (15.5%)*	*RR 0.84 (0.52 to 1.36)*	*25 fewer per 1000 (from 74 fewer to 56 more)*	*VERY LOW*
Post-thrombotic syndrome (at 8 years)	109/200 (54.5%)	107/200 (53.5%)	RR 1.02 (0.85 to 1.22)	11 more per 1000 (from 80 fewer to 118 more)	VERY LOW

10.2.1.2 Economic evidence

One study [211] was identified that compared observation only, long-term anticoagulant therapy and vena caval filter in patients with malignancies who either had an acute DVT or survived a PE. This is summarised in the economic evidence profile below (Table 63, and Table 63); evidence is presented separately for patients with DVT and patients with PE. See also the full study evidence tables in Appendix F.

Table 63: Vena caval filters vs no vena caval filters - Economic study characteristics

Study	Applicability	Limitations	Other Comments
Sarasin 2003[211]	Partially applicable (a)	Potentially serious limitations(b)	The population considered was patients with lung cancer. Lifetime horizon.

(a) Study from Switzerland and USA. Only patients with lung cancer were included. The type of filter used in the study is not routinely used anymore. Anticoagulation therapy has improved since time of study.

(b) Utilities estimated from expert opinion; source of funding not reported; indirect evidence on efficacy of filter vs. anticoagulation (both compared to no intervention in separate studies). No data was available on the incidence of PE in patients with cancer and DVT so it was assumed this was the same as in patients with no cancer. Unclear how studies for clinical parameters were identified and which study was eventually selected for base case values. A probabilistic sensitivity analysis was not conducted.

Table 64: Vena caval filters vs no vena caval filters - Economic summary of findings

Study	Incremental cost (£)	Incremental effects (Quality-Adjusted Life Months – [QALMs])	ICER	Uncertainty
Patients following an acute DVT				Threshold analysis: at values within clinically reasonable bounds observation was never cost-effective. If the probability of major bleeding with anticoagulant therapy is less than 0.5% per month, anticoagulation generates higher QALMs than vena caval filter. If effectiveness of vena caval filter is less than 75%, anticoagulation generates more QALMs. Results are not sensitive to the effectiveness of anticoagulants, mortality from untreated PE, discount rate.
Sarasin 2003[211]	Cost saving [a, b] -161 (vs anticoagulation) -490 (vs observation)	0.2 (vs anticoagulation) 1.2 (vs observation)	Vena caval filters dominate other strategies	
Patients surviving an initial PE				
Sarasin 2003[211]	Cost saving [a, b] -265 (vs anticoagulation) -1,160 (vs observation)	0.2 (vs anticoagulation) 2.0 (vs observation)	Vena caval filters dominate other strategies	

(a) 1989-1991 USD presented here as 1991 UK pounds, converted using 1991 Purchasing Power Parities. [177]

(b) Costs included were hospital cost of VTE, PE (fatal and non-fatal), long-term morbidity from major bleeding, short-term morbidity from major bleeding, fatal major bleeding, insertion of vena caval filter and death following insertion.

10.2.1.3 Evidence statements

Clinical **Vena caval filters**

In one study with 400 patients it was uncertain whether there was any clinically important difference in all cause mortality in the group treated with venal caval filters plus anticoagulation compared to the group treated with anticoagulation alone at 12 days, 2 years and 8 years (VERY LOW QUALITY).

In one study with 400 patients it is very uncertain whether there was a clinically important difference in incidence of PE between vena caval filters plus anticoagulation and anticoagulation alone in at 12 days (LOW QUALITY).

In one study with 400 patients there was a decrease which is likely to be clinically important in the number of patients with symptomatic PE in the group receiving vena caval filters plus anticoagulation compared to the group receiving anticoagulation alone at 2 years and at 8 years (VERY LOW QUALITY).

In one study with 400 patients it is very uncertain whether there was a clinically important difference in incidence of recurrent VTE in the group receiving vena caval filters plus anticoagulation compared to the group receiving anticoagulation alone at 2 years and at 8 years (VERY LOW QUALITY).

In one study with 400 patients there was a decrease which is likely to be clinically important in the number of people with symptomatic recurrent DVT in the group receiving anticoagulation alone compared to the group receiving vena caval filters plus anticoagulation at 2 years and 8 years (VERY LOW QUALITY).

In one study of 400 patients it is very uncertain whether there is a clinically important difference between vena caval filters plus anticoagulation and anticoagulation alone in major bleeding at 12 days, 2 years and 8 years (VERY LOW QUALITY).

In one study of 400 patients it is very uncertain whether there is any difference between vena caval filters plus anticoagulation and anticoagulation alone in post thrombotic syndrome (VERY LOW QUALITY).

Economic In patients with malignancy who had either a DVT or PE, vena caval filters are cost-effective compared to observation. This evidence has potentially serious limitations and partial applicability.

10.3 Graduated compression stockings

The term compression hosiery refers to two different products: anti-embolism stockings (AES) and graduated compression stockings (GCS). Although the terms AES and GCS are often used inter-changeably and both offer graduated compression they have different British and European Standards, different levels of compression and have different indications. AES are designed for the prevention of VTE in the immobile patient and GCS are designed for management and treatment of conditions such as venous leg ulcers and lymphoedema in the ambulant patient.

In this section, the safety and efficacy of GCS in the management of DVT and the prevention of PTS is discussed. GCS stockings are contraindicated in patients with 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 and Ankle:Brachial pressure index < 0.8, or cellulitis. Patients who use GCS to prevent PTS are expected to use it over a long period of time, and it is important to note that some of these contraindications develop over time in certain patient groups; for example patients with cancer may develop peripheral neuropathy after chemotherapy and develop oedema as the cancer progressed.

GCS may be either thigh length or below the knee and the length of stockings is a controversial issue. In our review potential difference in efficacy or safety between different types of compression stockings or lengths was investigated if evidence was found.

10.3.1 What is the effectiveness of graduated compression stockings to prevent post thrombotic syndrome in people with venous thromboembolic diseases?

No RCTs of thigh length graduated compression stockings were found. Two RCTs using knee length graduated compression hosiery in patients with proximal DVT were found. The first study used below knee ready-made elastic compression stockings with an ankle pressure of 30-40 mm Hg (Flebysan, Rovigo), started at discharge (5-10 days after admission), and patients were advised to use them at least during the day for a minimum of two years[198]. In the second study, patients received made-to-measure (Neodurelna Varitex) below-knee elastic compression stockings, with an ankle pressure of 40 mm Hg, started 2-3 weeks after the first episode of proximal DVT and continued for at least 2 years [26].

See clinical evidence tables in Appendix E.10, forest plots in Appendix G.6.2 and Economic evidence tables in Appendix F.

10.3.1.1 Clinical evidence

Table 65: Graduated compression stockings vs no graduated compression stockings – Quality assessment

Outcomes	No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Post-thrombotic Syndrome[26,198]	2	RCT	Serious limitations[(a)]	No serious inconsistency	No serious indirectness	No serious imprecision
Skin adverse events	0	RCT	-	-	-	-
Compliance	0	RCT	-	-	-	-
Fitting	0	RCT	-	-	-	-
Quality of life	0	RCT	-	-	-	-
VTE related mortality	0	RCT	-	-	-	-

(a) The outcome and method of measurement defined differently between the two studies. It was unclear how/whether the tool to diagnose PTS was validated before use in the study which contributed most of the information [26]. Both studies were open label, although outcome assessors were blinded to treatment assignment.

Table 66: Graduated compression stockings vs no graduated compression stockings - Clinical summary of findings

Outcomes	Stockings	No stockings	Relative risk (95% CI)	Absolute risk (95% CI)	Quality of evidence
Post-thrombotic Syndrome	42/186 (22.6%)	90/188 (47.9%)	RR 0.47 (0.35 to 0.64)	254 fewer per 1000 (from 172 to 311 fewer)	MODERATE

10.3.1.2 Economic evidence

No comparative studies were identified on the use of stockings to prevent PTS. However, one of the RCTs[198] included in the clinical review noted that the unit cost of stockings used in the study was 35 Euros. Patients had to use 4 stockings a year for a period of 2 years; therefore we calculated the total cost as 280 Euros (equal to 203 GBP, using the purchasing power parities[177]). No other use of resources was estimated in the study and the two arms were not subjected to a proper cost analysis.

10.3.1.3 Evidence statements

Clinical — In two studies of 374 patients there was a clinically important decrease in PTS in the group who wore graduated compression stockings over more than 2 years (started within 1-3 weeks of DVT onset) compared to group without stockings (MODERATE QUALITY).

No comparative data from RCTs were available for the following outcomes: skin adverse events; compliance; fitting; quality of life or VTE related mortality.

Economic — No economic evidence was found on this question. From a simple cost analysis based on a RCT, a 2-year treatment could cost approximately £200.

10.4 Recommendations and link to evidence

Recommendations	**23. Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications[(b)], and:** • **advise patients to continue wearing the stockings for at least 2 years** • **ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions.** • **advise patients that stockings need to be worn only on the affected leg or legs.** **(b)** Prescribers should refer to specific product information and contraindications before offering graduated compression stockings.
Relative values of different outcomes	Incidence of PTS was considered the most important outcome as this is the key contributor to morbidity and reduction of quality of life after a DVT, and severity of PTS is an important consideration. PTS is considered a more important outcome than adverse events such as skin problems or inconvenience to patients.
Trade off between clinical benefits and harms	The studies showed a clinically important (254 fewer per 1000 (95% CI 172 to 311 fewer) reduction in the incidence of PTS, but there were no comparative data on adverse events. The benefit from this reduction of PTS is likely to be more important to patients than the potential harms from adverse events such as skin disorders, or inconvenience to patients (adherence).
Economic considerations	Considering only the cost of stockings, a 2-year treatment could cost approximately £200 (based on a trial where 2 pairs of stockings were provided every 6 months). This cost was deemed to be offset by the reduction in incidence of PTS showed by the clinical review.
Quality of evidence	No RCTs of thigh length graduated compression stockings were found. Two RCTs using knee length graduated compression hosiery in patients with proximal DVT were found. Patients from both studies had their first episode of confirmed proximal DVT. Stockings were worn for a minimum of two years, starting within 1-3 weeks of DVT symptom onset. Both studies used properly fitted below the knee stockings. Follow up was between 36 to 90 months. The GRADE quality of evidence for the prevention of PTS outcome was moderate. Evidence was not available for all outcomes and there was no comparative evidence for adverse events. No economic evidence was found. A simple cost analysis was conducted.
Other considerations	The GDG considered the evidence about the efficacy and safety of graduated compressions stockings when wording the recommendation: • It was noted that the trials examined here used graduated compression hosiery that was over 30-40 mm Hg at the ankle. The GDG discussed what ankle pressure should be recommended. It was noted that adherence may be lower if the compression pressure is higher because they are more difficult to apply and remove and less comfortable to wear on a day to day basis. It was noted that the stockings indicated for prevention of PTS were either class III stockings, or class II stockings if poorly tolerated. Either British Class III stockings (25-35 mm Hg) or and European Class II (23-32 mm Hg)

Recommendations	**23. Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications[(b)], and:** • **advise patients to continue wearing the stockings for at least 2 years** • **ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions.** • **advise patients that stockings need to be worn only on the affected leg or legs.** **(b)** Prescribers should refer to specific product information and contraindications before offering graduated compression stockings.
	would be appropriate. The terminology 'over 23 mm Hg' was chosen so that any stocking above this pressure could be considered. The GDG agreed that it was better for a patient to wear stockings even if the pressure was lower than that used in the clinical trials. • The recommendation is made for a minimum of 2 years based on the trials reviewed. All used stockings for a minimum of 2 years, with good adherence recorded. The GDG were aware that trials are being conducted to investigate whether using stockings for only 6 months would be effective in patients without symptoms but data were not available at the time of review. Therefore, patients should be encouraged to continue using stockings for 2 years, until further trial information is available. • Whilst there is no evidence of further benefit of continuing graduated compression stockings in patients after two years, this would need to be an individual patient / doctor decision. However, graduated compression stockings may be required by patients to control their PTS symptoms beyond 2 years. This is more as a treatment of PTS rather than as prevention of PTS. • Knee length stockings were recommended because this is where the evidence was available. There was no evidence from RCTs about the effectiveness of thigh length stockings. Furthermore, thigh length stockings can be more difficult to fit and often roll down creating a tourniquet effect. However, clinical judgement, patient preference and adherence all important issues when deciding on stocking length, for example, some patients prefer full length stockings. Some flexibility should be allowed to fit the needs of different patients. • In the trials reviewed, patients were advised to use the stockings only in the affected limb, and to use the stockings as much as possible during the day or waking hours. Therefore, the GDG decided that the bullet point 'advise patients that stockings only need to be worn on affected leg' was added to the recommendation. In their clinical experience PTS would generally only occur in the symptomatic leg and it is therefore not necessary to wear stockings on both legs. However, If both legs are affected, stockings should be worn on both legs. This should be discussed with the patient. The GDG also discussed that patient preference should also be taken into consideration, for example, some patients may wish to wear stockings on both legs for comfort or aesthetic reasons. Patients should be encouraged to wear graduated compression stockings for as long as is practical in waking hours and to remove stockings when they go to bed. This allows for regular inspection of the skin and the use of emollient cream if

Recommendations	**23. Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications[(b)], and:** • **advise patients to continue wearing the stockings for at least 2 years** • **ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions.** • **advise patients that stockings need to be worn only on the affected leg or legs.** **(b)** Prescribers should refer to specific product information and contraindications before offering graduated compression stockings.
	required. The GDG discussed contraindications to the use of graduated compression stockings. This was not an area reviewed specifically and therefore specific recommendations were not formulated. However, a comprehensive list of contraindications had been listed for the use of antiembolism stockings (which are of a lower pressure, and typically worn over a relatively shorter period of time) for prophylaxis of VTE in the NICE guideline: Venous Thromboembolism: Reducing the Risk (CG92). The contraindications listed in the recommendation are relevant to patients using graduated compression stockings, and should be excluded before stockings are prescribed. The contraindications include: • suspected or proven peripheral arterial disease • peripheral arterial bypass grafting • peripheral neuropathy or other causes of sensory impairment • any local conditions in which stockings may cause damage, for example fragile 'tissue paper' skin, dermatitis, gangrene or recent skin graft • known allergy to material of manufacture • cardiac failure • severe leg oedema or pulmonary oedema from congestive heart failure • unusual leg size or shape • major limb deformity preventing correct fit. In addition, caution and clinical judgement should be used • when applying graduated compression stockings over venous ulcers or wounds. • When there are swelling or changes in leg sizes – patients should have their legs re-measured and graduated compression stockings refitted. The GDG discussed that patients may experience adverse events such as marking, blistering or discolouration of the skin, particularly over the heels and bony prominences, or pain and discomfort. In these situations, stockings should be discontinued and further medical advice obtained on whether a refitting is required or a discontinuation is more appropriate. The stockings are to be worn over two years. Practical considerations and patient adherence are important factors to ensure safe and effective use. Patients need to be aware of the reason the stockings were prescribed and

Recommendations	**23. Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications[(b)], and:** • **advise patients to continue wearing the stockings for at least 2 years** • **ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions.** • **advise patients that stockings need to be worn only on the affected leg or legs.** **(b)** Prescribers should refer to specific product information and contraindications before offering graduated compression stockings.
	how to use them correctly. A specific recommendation to provide patients using graduated compression stocking had been made for this guideline in the patient information section: "30. Advise patients about the correct application and use of below-knee graduated compression stockings, how long they should be worn and when they should be replaced." Please see section 11.3 for more information. In addition, the GDG considered a recommendation from Venous thromboembolism: reducing the risk (NICE clinical guideline 92) guideline about information that should be provided to patients to be applicable to patients who are using graduated compression stockings. Healthcare professionals should ensure that patients who receive graduated compression stockings • understand the benefits of wearing them • understand the need for daily hygiene removal • are able to remove and replace them, or have someone available who will be able to do this for them • know what to look for such as skin marking, blistering or discolouration, particularly over the heels and bony prominences • know who to contact if there is a problem. The GDG also agreed that at least a spare pair of stockings should be prescribed at any one time so that the patient has a pair to wear whilst the other one is being washed and dried. The GDG noted that in the RCT, patients always wore a pair of stockings and two pairs of stockings were prescribed. Stockings will also need replacing at appropriate intervals (every 3 to 6 months) to maintain their efficacy, and ideally the leg should be re-measured to ensure correct fit. If stockings become damaged, have apparent defects or do not return to their original shape on stretching, earlier replacement may be required. Patients need to be informed of the correct way to wash the stockings (hand washed at about 40°C and dried away from direct heat) as this can prolong the life of the stockings. To prevent skin problems and maintain hygiene during stockings use, patients need to be informed about when to take off the stockings, how often to wash them, and maintenance of hygiene of the legs.

Recommendations	**23. Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications[(b)], and:** • **advise patients to continue wearing the stockings for at least 2 years** • **ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions.** • **advise patients that stockings need to be worn only on the affected leg or legs.** **(b)** Prescribers should refer to specific product information and contraindications before offering graduated compression stockings.
	Potential equality issues include people with difficulty putting the stocking on. For these patients, an application aid may be helpful (information about these can be obtained from the manufacturer of the stocking or from specialist services). This recommendation was chosen as being a key priority for implementation. • It was chosen as a KPI because it was considered to have a high impact on outcomes important to patients and on reducing variation in care and patient outcome leading to more efficient use of NHS resources and promotes patient choice. Implementation support is required because there would be a change in service delivery, requires retraining of professionals or development of new skills and competencies and needs to be implemented across various agencies or setting.

Recommendations	**24. Offer temporary inferior vena caval filters to patients with proximal DVT or PE who cannot have anticoagulation treatment, and remove the inferior vena caval filter when the patient becomes eligible for anticoagulation treatment.**
Relative values of different outcomes	The risk of mortality was considered the most important outcomes. The risk of PE, major bleeding, DVT and PTS were all considered to be important outcomes.
Trade off between clinical benefits and harms	The benefit of avoiding a PE or a recurrent PE was considered against the risk of increased bleeding. There is no evidence available from this population. It was considered that without any anticoagulation some form intervention may still be required to prevent PEs and deaths. IVC filter is not the best option when anticoagulation is available; IVCs should be removed when anticoagulation is available. The risk of DVT and PTS could increase with the placement of IVC filters.
Economic considerations	In patients with malignancy, vena caval filters were cost-effective compared to observation in patients with DVT or PE.
Quality of evidence	No evidence was available for IVC filters in patients who cannot have anticoagulation. Only one RCT was found in the use of IVC filter, and this was conducted in patients who were eligible for anticoagulants. There was a potential reduction of PE with IVC filter, but the evidence was not really

Recommendations	**24. Offer temporary inferior vena caval filters to patients with proximal DVT or PE who cannot have anticoagulation treatment, and remove the inferior vena caval filter when the patient becomes eligible for anticoagulation treatment.**
	relevant, as it was conducted in an older study population and mortality was due to cancer and other causes. The literature was not relevant to the context of practice in 2011 as they included permanent rather than temporary filters. The economic evidence has potentially serious limitations and partial applicability. This recommendation was developed based on GDG consensus.
Other considerations	The risk of mortality from PE was considered to be high when left untreated. Some patients may not be able to tolerate anticoagulation because of excessive bleeding. The GDG's experience was that modern filters can be removed and should be removed as soon as anticoagulation can be started. There are significant risks when filters are left in place for too long, for example they can become more difficult to remove when left for a longer period. The GDG discussed circumstances where an IVC filter may be considered. For example, if the patient has had a recent gastrointestinal bleed or a haemorrhagic stroke, anticoagulation significantly increases the risk of a repeat bleed or stroke and hence the use of an IVC filter should be considered. Another patient group in which the insertion of temporary IVC filter should be considered in those requiring surgery, where again the risk of bleeding is high. Others that may be unsuitable for anticoagulation are those prone to falls or injury, those unable or unwilling to attend anticoagulation clinics or to have the careful regulation of their anticoagulation therapy performed.

Recommendations	**25. Consider inferior vena caval filters for patients with recurrent proximal DVT or PE despite adequate anticoagulation treatment only after considering alternative treatments such as:** • **increasing target INR to 3-4 for long-term high-intensity oral anticoagulant therapy or** • **switching treatment to LMWH.**
Relative values of different outcomes	The risk of mortality, the risk of recurrent PE and the risk of major bleeding were all considered to be important outcomes. The risk of recurrent PE was considered to be the most important of these outcomes. The risk of DVT increases with the placement of IVC filters
Trade off between clinical benefits and harms	The benefit of avoiding a PE or a recurrent PE, was compared to the risk of increased bleeding, and risk of DVT.
Economic considerations	No economic evidence was found for patients who have recurrent VTE despite adequate anticoagulation treatment. Both IVC filter and oral anticoagulant therapy are associated with costs. The recommendation was based mainly on clinical reasons.
Quality of evidence	No evidence was available for temporary filters. The evidence available was in

Recommendations	**25. Consider inferior vena caval filters for patients with recurrent proximal DVT or PE despite adequate anticoagulation treatment only after considering alternative treatments such as:** • **increasing target INR to 3-4 for long-term high-intensity oral anticoagulant therapy or** • **switching treatment to LMWH.**
	permanent filters This recommendation was developed based on GDG consensus.
Other considerations	Some patients may have recurrent VTE despite adequate anticoagulation. This recommendation is a 'consider' recommendation because there is no evidence relating to current practice with temporary filters. The GDG discussed that in regards to a patients' quality of life, the insertion of a filter may be preferable to lifelong injections of anticoagulation for some patients, although this must be balanced against the higher risk of DVT and PTS.

Recommendations	**26. Ensure that a strategy for removing the inferior vena caval filter at the earliest possible opportunity is planned and documented when the filter is placed, and that the strategy is reviewed regularly.**
Relative values of different outcomes	The risk of mortality, recurrent PE and major bleeding were all considered to be important outcomes. The risk of mortality was considered to be the most important of these outcomes.
Trade off between clinical benefits and harms	The benefit of avoiding a recurrent PE was balanced against the risk of increased bleeding.
Economic considerations	There are clinical issues associated with keeping the filters in for a long time; filters could affect patients' quality of life and removing them at the earliest opportunity would minimise the detriment on quality of life.
Quality of evidence	There is no direct evidence for this. This is a supporting recommendation, it was developed based on GDG consensus.
Other considerations	Placement of inferior vena cava filter may prevent PE but will not help manage DVT and can often make swollen leg worse. These filters can also get clogged up with clots and therefore increase the risk of PTS. The GDG highlighted that many filters are forgotten and left in situ. Therefore, at the time of insertion of IVC filters, there should be a clear management plan including the indication for insertion, the intended length of time that the filter is likely to be necessary and the intended point at which the filter's removal should be performed. As circumstances change, this management plan should be reviewed. For example, in a patient needing surgery and hence unsuitable for immediate anticoagulation, at the time of insertion the date for filter removal should be organised, with a plan in place for the commencement of anticoagulation as appropriate. Filters become more difficult to remove when they have been left in for a longer period of time. The risk of endothelialisation of the struts into the IVC filter wall increases with time and the GDG thought that ideally there should

Recommendations	**26. Ensure that a strategy for removing the inferior vena caval filter at the earliest possible opportunity is planned and documented when the filter is placed, and that the strategy is reviewed regularly.**
	be a plan to remove temporary IVC filters as soon as clinically possible, usually within 1-2 week of an operation.

11 Patient information

11.1 Introduction

The provision of information and support about the management of VTE has the potential to improve patient outcomes by giving patients the opportunity to become active in the management of their condition. This provision can come in many forms and may be tailored to the requirements of certain sub-groups of patients such as those with cancer.

Patients value appropriate explanation and information regarding their medical condition. VTE is a common, clinically important disease. Therapies are often long-term or complex. The provision of patient information is good medical practice as it has the potential to improve patient adherence and facilitate patient empowerment. It may also aid the prevention of further VTE events by informing patients about suitable preventative measures. This information should be provided in the most appropriate way for each patient. In this chapter, we look at whether there is any evidence that the provision of patient information and support may improve patient outcomes.

11.2 Patient information

11.2.1 Does the provision of information and support about the management of VTE improve patient outcomes?

Three RCTS were found which studied more intensive patient information provision compared to control groups (where patients had the "standard" or "usual" care and information within their own settings) in patients using a VKA. None of the studies were conducted in the UK and they all had differences in the content, method of delivery and intensity of the education in the intervention and information groups.

See clinical evidence tables in Appendix E.14, forest plots in Appendix G.8.

11.2.1.1 Clinical evidence

Table 67: Patient information vs usual care – Quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Recurrent VTE[134,187]	2	RCT	Serious limitations[(a)]	No serious inconsistency	Serious indirectness[(b)]	Serious imprecision[(c)]
Major bleeding[134,187]	2	RCT	Serious limitations[(a)]	No serious inconsistency	Serious indirectness[(b)]	Very serious imprecision[(c)]
Perception of patients (knowledge)[187]	1	RCT	Serious limitations[(a,e)]	No serious inconsistency	Serious indirectness[(b)]	No serious imprecision
Compliance: % Pill count relative to prescribed dose[134]	1	RCT	Serious limitations[(a)]	No serious inconsistency	Serious indirectness[(a)]	No serious imprecision
Percentage of time within target INR						
Subgroup: Brochure vs no	*1*	*RCT*	*Serious limitations*	*No serious inconsistency*	*Serious indirectness*	*No serious imprecision*

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
intervention [17]			(a),(d)		(b)	
Subgroup: Course (group education) vs no intervention [17]	*1*	*RCT*	*Serious limitations*(d)	*No serious inconsistency*	*Serious indirectness* (b)	*No serious imprecision*
Subgroup: Course (group education) vs brochure [17]	*1*	*RCT*	*Serious limitations*(d)	*No serious inconsistency*	*Serious indirectness* (b)	*No serious imprecision*
Subgroup: Intensive individual[134]	*1*	*RCT*	*Serious limitations*(a)	*No serious inconsistency*	*Serious indirectness* (b)	*No serious imprecision*
PTS	0	-	-	-	-	-
Quality of life	0	-	-	-	-	-
Patient satisfaction	0	-	-	-	-	-

(a) One study, which contributed to most of the information, had cluster randomisation[187]. The other study was conducted as part of the factorial design to compare two oral anticoagulants. An electronic bottle recorded the exact date and time of opening.[134]

(b) The studies were conducted in France and Italy. The types and levels of information provided in the control and intervention arms differ between studies. It was unclear whether the information provided in the control arms would be different from that provided in the UK. Time within INR target is also a surrogate marker for patient outcome. The GDG considered a change of about 10% to be potentially clinically important.

(c) The CIs were wide, and the CIs cross thresholds of important benefits and important harms.

(d) Randomisation method was unclear [17].

(e) For the knowledge outcome: the maximum point was 20 points and it was unclear whether the questionnaire was validated. It is uncertain how the data should be interpreted.

Table 68: Patient information vs Usual care - Clinical summary of findings

Outcome	Intensive Information	Usual care	Relative risk (95% CI)	Absolute effect	Quality
Recurrent VTE (a)	3/202 (1.5%)	4/185 (2.2%)	RR 0.72 (0.14 to 3.72)	6 fewer per 1000 (from 19 fewer to 59 more)	VERY LOW
Major bleeding(a)	1/102 (0.98%)	1/185 (0.54%)	RR 0.59 (0.17 to 2.02)	2 fewer per 1000 (from 4 fewer to 6 more)	VERY LOW
Perception of patients (knowledge)	N=160	N=142	-	MD 1.5 higher (0.43 to 2.57 higher)	LOW
Compliance: % Pill count relative to prescribed dose	N=42	N=43	-	MD 0.3 higher (6.82 lower to 7.42 higher)	LOW
Percentage of time within target INR					
Subgroup: Brochure vs no intervention	*N=75*	*N=77*	-	*MD 4 lower (10.58 lower to 2.58 higher)*	*LOW*
Subgroup: Course (group education) vs no intervention	*N=66*	*N=77*	-	*MD 2 lower (8.28 lower to 4.28 higher)*	*LOW*
Subgroup: Course (group education) vs brochure	*N=66*	*N=75*	-	*MD 2 higher (5.1 lower to 9.1 higher)*	*LOW*
Subgroup: Intensive individual education vs usual care	*N=39*	*N=42*	-	*MD 4.2 lower (11.89 lower to 3.49 higher)*	*LOW*

(a) Random effect analysis was conducted due to differences in interventions and control groups between studies.

11.2.1.2 Economic evidence

No economic evidence was found on this question.

11.2.1.3 Evidence statements

Clinical	In two studies with 387 patients it is very uncertain whether there is a clinically important difference in the number of people with recurrent VTE between the intensive information group and the usual care group (VERY LOW QUALITY). In two studies of 287 patients it is it is unlikely there is a clinically important difference in major bleeding between the group receiving intensive education and the group receiving usual care (VERY LOW QUALITY). In one study of 302 patients it is unlikely that there is any difference of clinical importance in patient knowledge in the group receiving tailored intensive education compared to the group receiving usual care (LOW QUALITY). In one study of 85 patients it is unlikely that there is any difference of clinical importance in compliance in the group receiving intensive education compared to the group receiving usual care (LOW QUALITY). In one study of 152 patients it is unlikely that there is any difference of clinical importance in the percentage time spent within target INR in the group receiving brochures compared to the group receiving no intervention (LOW QUALITY). In one study of 143 patients it is unlikely that there is any difference of clinical importance in the percentage time spent within target INR in the group receiving a course (group education) compared to the group receiving no intervention (LOW QUALITY). In one study of 141 patients it is unlikely that there is any difference of clinical importance in the percentage time spent within target INR in the group receiving a course (group education) compared to the group receiving brochures (LOW QUALITY). In one study of 81 patients it is unlikely that there is any difference of clinical importance in the percentage time spent within target INR in the group receiving intensive individual education compared to the group receiving usual care (LOW QUALITY).
Economic	No economic evidence was found on this question.

11.3 Recommendations and link to evidence

Recommendations	**27. Give patients having anticoagulation treatment verbal and written information about:** • **how to use anticoagulants** • **duration of anticoagulation treatment** • **possible side effects of anticoagulant treatment and what to do if these occur** • **the effects of other medications, foods and alcohol on oral anticoagulation treatment** • **monitoring their anticoagulant treatment** • **how anticoagulants may affect their dental treatment** • **taking anticoagulants if they are planning pregnancy or become pregnant** • **how anticoagulants may affect activities such as sports and travel** • **when and how to seek medical help.**
Relative values of different outcomes	Patient perception (including knowledge and attitude) of their condition was felt to be the most important outcome by the GDG, followed by quality of life, recurrent VTE, major bleeding, percentage time in therapeutic range and post-thrombotic syndrome.
Trade off between clinical benefits and harms	Providing education to patients about their condition could increase patient knowledge and awareness and potentially lead to improved patient outcomes. Appropriate patient information is part of good medical practice and may have positive outcomes such as increased patient satisfaction and improvement in quality of life which may not be reported in the evidence reviewed. The GDG considered this potential improvement in outcomes to outweigh any time or cost associated with providing this information. Furthermore, improved understanding of treatment has the potential to reduce anxiety and improve patient participation. However, there is potential for harm if this information is not provided, for example, resulting in low adherence with anticoagulant treatment or delay in seeking medical help due to lack of awareness of side effects.
Economic considerations	No economic evidence was found for this question. Providing patients with relevant information is not considered to generate significant costs and could lead to a more efficient use of resources, for example patients making the most efficient use of treatment.
Quality of evidence	It is particularly difficult to interpret studies on the impact of information provision. Information provision could only be expected to be effective if the information is relevant, acceptable to patients and provided using an effective medium. The only outcomes where evidence was found were; the percentage of time within target INR range, recurrent VTE, compliance and patient knowledge. The quality of evidence for these outcomes was of either low or very low quality. Many outcomes identified as important by the GDG were not reported. The evidence was mostly from studies in patients using VKA in European countries other than the UK. Each study had different types and intensity of

Recommendations	**27. Give patients having anticoagulation treatment verbal and written information about:** • **how to use anticoagulants** • **duration of anticoagulation treatment** • **possible side effects of anticoagulant treatment and what to do if these occur** • **the effects of other medications, foods and alcohol on oral anticoagulation treatment** • **monitoring their anticoagulant treatment** • **how anticoagulants may affect their dental treatment** • **taking anticoagulants if they are planning pregnancy or become pregnant** • **how anticoagulants may affect activities such as sports and travel** • **when and how to seek medical help.**
	information provided in the control and intervention groups. It is uncertain whether the evidence is directly applicable to VTE patients in the UK. In addition, it is difficult to interpret the clinical importance of outcomes, for example, a difference in the percentage of time that INR was within target range or knowledge score (how much difference between arms would be clinically important?) There were also serious limitations in how the studies were designed and conducted. No economic evidence was available on this question.
Other considerations	Information should be appropriate to individual patients and be sensitive to those with visual or hearing impairment, physical or learning disabilities. Language barriers, such as difficulties with reading, understanding or speaking English should not be a reason for non-provision of information. Provision on a national basis of translated documents should be undertaken. A source of further information as required is suggested. For patients with cancer, information that is relevant to them, such as the increased risk of recurrent VTE in people with cancer should be discussed. The GDG were aware that there are already sources of information available for patients who take oral anticoagulation. For example, the National Patient Safety Agency have produced a booklet titled 'Actions that can make oral anticoagulant therapy safer: Information for patients and carers' [169]. Nevertheless, it is important to tailor information to the needs of individual patients. Although the evidence found was only for patients prescribed VKA the recommendation is also applicable for patients prescribed LMWH. The GDG discussed that it may be difficult for patients (or carers) to commence personal injections (or injecting another person) and that they may need support and training in order to do so. The GDG also discussed the importance of emphasising the safe disposal of sharps to the patient, but felt this was covered in another guideline- CG02, Infection Prevention and Control in the Community Setting [166]. This was discussed as a potential key priority for implementation as some GDG members felt that not all patients were receiving the required information.

Recommendations	**28. Provide patients who are having anticoagulation treatment with an 'anticoagulant information booklet' and an 'anticoagulant alert card' and advise them to carry the 'anticoagulant alert card' at all times.**
Relative values of different outcomes	Major bleeding and the associated mortality and morbidity were considered the most important outcomes, as well as improving quality of life for patients by providing security and reassurance in case of an accident/ emergency.
Trade off between clinical benefits and harms	Patients who are taking anticoagulants are at an increased risk of bleeding. In the event of major trauma or where there is difficulty in verbal communication, carrying an anticoagulant alert card can help to ensure that appropriate care is provided. Some patients may consider it inconvenient, but this is greatly outweighed by the benefits of carrying the card.
Economic considerations	No economic evidence was found on this question. This recommendation is not expected to be associated with increased costs.
Quality of evidence	Non-applicable
Other considerations	The GDG considered this to be an example of good medical practice. To improve the adherence of carrying the card it is important to explain the rationale and the benefit of carrying the card to patients. Recommendations are based on GDG consensus.

Recommendations	**29. Be aware that heparins are of animal origin and this may be of concern to some patients*. For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement after discussing their suitability, advantages and disadvantages with the patient. [This recommendation is from Venous thromboembolism: reducing the risk (NICE clinical guideline 92)].** *** See "Religion or belief: a practical guide for the NHS", website: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093133)**
Relative values of different outcomes	Please refer to Venous thromboembolism: reducing the risk (NICE clinical guideline 92).Patient preferences or patient views were the most important outcomes.
Trade off between clinical benefits and harms	Please refer to Venous thromboembolism: reducing the risk (NICE clinical guideline 92). Ideally, the choice of agent should be based on the most evidence-based and cost-effective agent for a given population. However, in situations where there are strong patient concerns, these need to be discussed openly.
Economic considerations	Non-applicable
Quality of evidence	Non-applicable
Other considerations	While it is important to offer patients alternatives if there are concerns about using animal based products, it is also important that patients are aware of the clinical benefits or disadvantages (if any) of using these alternative products. If religious beliefs are a source of concern, the patients should be aware of the official stand of religious bodies about the product. Patients will only be able to make a good decision if they have a complete picture of the pros and cons of

Recommendations	**29. Be aware that heparins are of animal origin and this may be of concern to some patients*. For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement after discussing their suitability, advantages and disadvantages with the patient. [This recommendation is from Venous thromboembolism: reducing the risk (NICE clinical guideline 92)].** *** See "Religion or belief: a practical guide for the NHS", website: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093133)**
	using these products. Where information is available, it will be useful to direct the patients to these information sources. There is information for patients with specific concerns e.g: "Porcine Derived Products" booklet which is referred to in the Department of Health document titled" Religion or belief: a practical guide for the NHS" (available from http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093133) . If the relative risks and benefits are explained to the patient and the decisions clearly documented in the patient's notes, the patient is perfectly within their rights to choose a less effective option, however difficult that might be for the clinician who wants to provide the best care.

Recommendations	**30. Advise patients about the correct application and use of below-knee graduated compression stockings, how long they should be worn and when they should be replaced.**
Relative values of different outcomes	The GDG considered the most important outcomes to be; the correct use of stockings to ensure the effective prevention of PTS, and safe use of stockings It was felt that these could impact quality of life and adherence to the treatment. Other outcomes such as patient satisfaction and knowledge were acknowledged as being important.
Trade off between clinical benefits and harms	Providing information to patients regarding the correct application, use and duration of stockings may help to ensure that they are worn correctly, and therefore prevent side effects associated with stocking use, such as skin problems and blisters. Information may also help adherence in using stockings and allow them to be effectively used to prevent PTS. It may also provide reassurance to patients that they are correctly managing their condition.
Economic considerations	No economic evidence was found on this question. Providing patients with relevant information is not considered to generate significant costs. Instead it could lead to a more efficient use of resources as patients make the most efficient use of treatment.
Quality of evidence	No clinical or economic evidence was found.
Other considerations	For stockings to be fully effective and safely used, patients should be aware of their correct application, use and potential deleterious effects of poorly fitting stockings. They also need to be aware of the benefits of using the stockings, and the importance of using the stockings for the recommended duration. Graduated compression stockings for the prevention of PTS need to be worn

Recommendations	**30. Advise patients about the correct application and use of below-knee graduated compression stockings, how long they should be worn and when they should be replaced.**
	for at least two years, and are at a higher compression pressure than those used for the prophylaxis of VTE. Therefore even more caution should be applied, and patients should be advised properly. Consideration should also be given to the refitting of stockings. The GDG discussed the fact that patients may not be aware of basic information about how to wear their stockings correctly. Patients should be advised that they do not need to wear their stockings at night and of the importance of hygiene. Special considerations may need to be given to patients who are elderly, frail or have physical disabilities as they may find it difficult to apply and remove stockings. In addition, the GDG considered that recommendations from the NICE guideline; Venous thromboembolism: reducing the risk (NICE clinical guideline 92) about information to be provided to patients is also applicable to patients who are using graduated compression stockings. Healthcare professionals should ensure that patients who receive graduated compression stockings: • understand the benefits of wearing them • understand the need for daily hygiene removal • are able to remove and replace them, or have someone available who will be able to do this for them • know what to look for such as skin marking, blistering or discolouration, particularly over the heels and bony prominences • know who to contact if there is a problem. This recommendation is based on best practice and GDG consensus. The GDG had taken into account the information obtained from the review of efficacy of graduated compression stockings within this guideline. This recommendation supported the recommendation on graduated compression stockings (recommendation 26).

12 Self-management and self-monitoring for patients treated with a vitamin K antagonist

12.1 Introduction

Until recently VKAs, such as warfarin, have been the only oral anticoagulants available for clinical use. VKAs have highly unpredictable pharmacokinetics, and therefore their anticoagulant effect requires monitoring. The unpredictability of their pharmacokinetics is multifactorial, including; genetic differences in enzymes such as cytochrome p450 that metabolise VKA, environmental factors such as changes in dietary intake or absorption of vitamin K or the concurrent use of other medication that interferes with VKA uptake or metabolism. If the anticoagulation effect is higher than required there is an increased risk of bleeding and if it is too low there is a potential lack of therapeutic benefit.

VKA dosage can be adjusted appropriately based on monitoring results. The effect of VKA is measured by the ratio of the prolongation of the patient's prothrombin time compared to a normal prothrombin time. Because of differences in performing the assay, this has been standardised to the International Normalised Ratio (INR). Keeping the INR in the target range is important as VKAs have a narrow therapeutic window with an annual risk of major bleeding of 0.5% per year.[139]

Approximately one million individuals receive VKA in the United Kingdom.[40] Attending and running anticoagulant clinics is costly in time and money for both patients and the health service. Improvements in technology have resulted in small hand-held devices that can perform near–patient INR testing using a blood sample from a finger prick. These small hand-held devices are often referred to as point of care testing (POCT) devices, which includes an array of devices where the tests can be conducted near the patient, without having to send samples to a laboratory. These devices rely on a number of factors; the patient being able to squeeze blood from their finger tips (not possible for all patients); they require quality control against "gold standard" laboratory testing; and there must not be a condition which can interfere with the INR testing which is a problem for some patients with antiphospholipid syndrome.

These POCT devices enable patients to run testing of their own INR without attending clinics (self monitoring). In addition, they also offer total independence for patients who are able to adjust the dose of VKAs themselves (self management). Patients that undertake self monitoring, work in partnership with health professionals, who advise about the dose of daily VKA administration, usually over the telephone. Patients who undertake self management are able to adjust daily doses of VKA themselves after training.

The commonest indication for VKAs is the prevention of stroke in patients with atrial fibrillation, thus much of the data on self management and self monitoring comes from these patients. However, there is no reason why this data cannot be extrapolated to patients who are receiving VKA to prevent recurrent VTE.

The term "usual care" has been used to describe the care received by the control group in the clinical evidence for this chapter. This is because all of the control groups in the included studies use a form of anticoagulation clinical care; however the type of anticoagulation service used as a control, frequency of clinic visits and anticoagulation education received varies between the included studies.

12.1.1 What is the effectiveness of self monitoring or self management compared to hospital/GP testing for long-term pharmacological treatments?

See clinical evidence tables in Appendix E.14, forest plots in Appendix G.8 and Economic evidence tables in Appendix F.

12.1.1.1 Clinical evidence

One Cochrane systematic review[75] was identified that included 18 randomised controlled trials. Eleven studies compared INR self management[35,41,70,71,132,159,212,225,226,239,256] with routine laboratory monitoring, six studies compared INR self monitoring[24,76,94,113,121,265] with routine laboratory monitoring and one study compared self management and self monitoring with routine laboratory monitoring.[74]

There were important features and variations in the studies included in the systematic review which need to be taken into considerations:

- Population; people with atrial fibrillation and people undergoing heart valve implantation were recruited in all studies
- Training received for monitoring device. There were variations in the intensity and duration of training that people received to enable the use of the point of care testing device
- Overall education and training about anticoagulation. There were variations in whether the intervention and usual care groups received training. If people included in the study did receive training, the type, amount and delivery varied between studies. Some studies included quite a lot of training; for example one study[46] gave both the intervention and usual care group 3 to 6 sessions of training. Many studies did not state how much or what sort of training was given to people in the intervention or usual care groups. Information with regards to training was frequently not reported for the usual care group.

Table 69: Self monitoring or self management vs routine laboratory monitoring– quality assessment

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Recurrent VTE[24,70,71,159,210,212,256]	7	RCT	Serious limitations (a, h)	Serious inconsistency(f)	Serious indirectness(d,h)	Serious imprecision(e)
Major Bleeding[24,41,46,63,70,71,74,94,113,121,132,157,159,210,213,225,226,240,256,265]	21	RCT	Serious limitations (a, b, c)	No serious inconsistency	Serious indirectness(d)	Serious imprecision (e)
Minor Bleeding						
Subgroup-minor Bleeding-self management (i)41,70,71,159,212,225	*6*	*RCT*	*Serious limitations* (a)	*Serious inconsistency*(f)	*Serious indirectness*(d)	*Serious imprecision* (e)

Subgroup-minor Bleeding-self monitoring *(i)46,76,113,121,157,265*	*6*	*RCT*	*Serious limitations* (a)	*Serious inconsistency* (f)	*Serious indirectness* (d)	*Serious imprecision* (e)
Percentage of time INR in range						
Subgroup-percentage of time INR in range-self management *(i)35,70,71,159,225,226,239*	*7*	*RCT*	*Serious limitations*(b)	*Serious inconsistency*(f)	*No serious indirectness*	*Serious imprecision* (e)
Subgroup-percentage of time INR in range-self monitoring *(i)*24,46,76,113,121,157,210,265	*8*	*RCT*	*Serious limitations* (a, b)	*Serious inconsistency*(f)	*No serious indirectness*	*No serious imprecision*
% of INR measurements out of range 41,63,70,71,74,94,113,132,159,210,212,225,240,256,265	15	RCT	Serious limitations(a, b)	No serious inconsistency	No serious indirectness	Very serious imprecision (g)

(a) Randomisation, allocation concealment or blinding not reported.

(b) One large study with 2922 patients contributed to most of the information. It was unclear whether ITT analysis was used and the drop- out rate was also unclear[157] For various other studies it was unclear whether ITT analysis was used, and they also had unclear reporting of numbers of dropouts or large numbers of dropouts.

(c) Six studies had no definition of major bleeding [63,74,94,113,121,157]. Six studies reported adverse events individually and described occurrences of bleeding but did not define major bleeding, and the 8 studies that provided a definition of major bleeding had minor variation in the definition of major bleeding.

(d) The population included a mixture of people with VTE, atrial fibrillation or people undergoing heart valve implantation. The range of patients with VTE ranged from 7.1- 64 % in these studies. The average age of this population was 61.9 years, which is older than most VTE populations. The GDG noted that these patients are at a higher risk of bleeding.

(e) CI crosses MID making the effect size uncertain. For the percentage of INR within outcome, the GDG decided that the MID is about 10%. In addition, there were 7 studies (3 in self management subgroup and 4 in self monitoring subgroup) where data cannot be pooled.

(f) Heterogeneity within and/ or between groups. Subgroup heterogeneity was apparent in the outcome recurrent VTE (I2= 47 %) and subgroup heterogeneity was significant for the outcome percentage of time INR in range (I2= 77.4 %). I2 values for overall heterogeneity were significant for minor bleeding (I2= 80 %) and for percentage of time INR in range (I2= 95%). All outcomes were analysed using random effects.

(g) 11 out of 15 studies reported percentage of INR in range therefore percentage of INR out of range calculated by NCGC for these studies. This data could not be pooled or meta-analysed.

(h) Few studies reported recurrent VTE as a direct outcome due to the varying population, therefore sparse data was available. Most data obtained was extracted from those papers that reported individual thomboembolic events. Furthermore, of the studies that did report this as an outcome, there were large numbers lost to follow-up, one trial was a crossover trial and one trial was stopped early.

(i) Subgroup analysis of 2 pre-specified subgroups for the percentage of time INR in range and minor bleeding outcome was carried out due to heterogeneity between subgroups.

Table 70: Self monitoring or self management vs routine laboratory monitoring - Clinical summary of findings

Outcome	*Self monitoring or self management*	*Usual care*	*Relative Risk*	*Absolute effect*	*Quality*
Recurrent VTE	3/1237 (0.2%)	3/1182 (0.3%)	RR 0.83 (0.16 to 4.2)	0 fewer per 1000 (from 2 fewer to 8 more)	VERY LOW
Major Bleeding	262/4379 (6%)	261/4262 (6.1%)	RR 0.97 (0.82 to 1.14)	2 fewer per 1000 (from 11 fewer to 9 more)	LOW
Minor Bleeding [(b)]					
Subgroup: Minor Bleeding- self management	*77/894 (8.6%)*	*150/854 (17.6%)*	*RR 0.91 (0.39 to 2.13)*	*16 fewer per 1000 (from 107 fewer to 198 more)*	*VERY LOW*
Subgroup: Minor Bleeding- self monitoring [(d)]	*376/1696 (22.2%)*	*326/1675 (19.5%)*	*RR 1.02 (0.76 to 1.36)*	*4 more per 1000 (from 47 fewer to 70 more)*	*VERY LOW*
Percentage of time INR in range[(c)]					
Subgroup- percentage of time INR in range- (self management) [(b), (c)]	*70% (mean) N=804*	*68.3% (mean) N=745*	-	*MD 2.5 higher (3.24 lower to 8.23 higher)*	*VERY LOW*
Subgroup- percentage of time INR in range- (self monitoring) [(b), (c)]	*70.1% (mean) N=1586*	*72.9% (mean) N=1572*	-	*MD 3.77 lower (4.87 to 2.67 lower)*	*LOW*
Percentage of INR measurements out of range	[(a)]	[(a)]	[(a)] range from 1.7 % to 77.7%	[(a)]	VERY LOW

(a) Could not be calculated as data could not be pooled

(b) Subgroup analysis of 2 pre-specified subgroups for the percentage of time INR in range outcome was carried out due to large heterogeneity between subgroups

(c) The Standard mean difference for percentage of time INR in range, percentage of time INR in range- (self management) and percentage of time INR in range- (self monitoring) was 0.08 (-0.20, 0.36), 0.35 (-0.16, 0.86) and -0.24 (-0.31, -0.17) respectively. This indicates that it is unlikely that there is a clinically important difference between INR self monitoring or self management and routine laboratory monitoring. For subgroup- percentage of time INR in range- (self monitoring) the effect size is likely to be too small to be clinically important

(d) Unpublished data from one study [113] was included in the Cochrane review, but sensitivity analysis was conducted for this study in all outcomes. The inclusion of this study did not make an important change in most outcomes, with the exception of minor bleeding, where the RR changed from 1.02 [0.76, 1.36] to 0.89 [0.47, 1.68] for the self monitoring subgroup with the removal of the unpublished data from the Kaatz study.

(e) Random effects analysis were carried out for all the analysis in this section. The GDG decided there were too many variations in the population, intervention and comparison of the studies pooled. The underlying assumption of fixed

effects, which assumed that all the studies were measuring the effects is violated. Random effects model, which took into account random variations between studies and within studies was considered a more appropriate conservative measure and results were reported here. Sensitivity tests were conducted with fixed effect model to ensure no important variations which could change decision making.

(f) Due to the large variations between studies, random effects analysis was used for all outcomes, because this model assumes there were random variations between studies and within study instead of assuming that all the studies were measuring the same effect (as in fixed effect model). However, random effects analysis gave larger weights to smaller studies; giving unpublished data from a study by Kaatz2001 which was included in the Cochrane review more weight than if conducted as a fixed effect analysis. This study had severe limitations, and therefore sensitivity analyses excluding the unpublished data from Kaatz2001was conducted. The exclusion of unpublished data from Kaatz2001 did not make an important change except for minor bleeding outcome.

12.1.1.2 Economic evidence

Two UK studies were used that included the relevant comparison.[40,112] These are summarised in the economic evidence profile below (Table 71 and Table 72). Both studies are based on the results of the SMART trial which was included in the Cochrane systematic review reported in 12.1.1.1. See also the full study evidence tables in Appendix F.

One study[241] was excluded because it was only partially applicable (cost from Germany and no measure of effectiveness was assessed).

Table 71: Self-monitoring or self-management versus usual care – Economic study characteristics

Study	Limitations	Applicability	Other comments
Connock 2007[40]	Minor limitations[(a)]	Partially applicable[(b)]	Markov model where first year outcomes are based on the SMART trial. 10 year time horizon.
Jowett 2006[112]	Minor limitations[(c)]	Partially applicable[(b)]	Based on the SMART trial. 1 year follow-up.

(a) Results are reported only incrementally.

(b) The population included is patients requiring anticoagulation, not only patients with VTE. The intervention compared is self-management, not self-monitoring.

(c) Short follow-up time (1 year)

Table 72: Self-monitoring or self-management versus usual care – Economic summary of findings

Study	Incremental cost per patient (£)	Incremental effects per patient (QALYs)	ICER (£/QALY)	Uncertainty
Connock 2007[40]	1,004[(a, b)]	0.01577[(b)]	63,665[(b)]	Probability cost-effective: 44% When time horizon considered was 5 years, ICER = £122,365 per QALY.
Jowett 2006[112]	295[(c, d)]	0.009[(d)]	32,778[(d)]	Probability cost-effective: 30% If patients' costs are included, ICER = £31437 per QALY gained. Probability cost-effective: 32% Using complete case utility values, ICER = £295,000 per QALY gained. Probability cost-effective: 16% Patient self-management cost was still significantly higher than usual care when the lifetime of the machine was changed to 5 or 10 years or when the training costs were excluded.

(a) 2005 GBP. Costs incorporated are: Cost of training for PSM and CoaguCheck machine (for the first year only), GP consultation (x2), internal (x4) and external (x1) quality control, test strip (x26). Cost of acute events (major and minor bleeding, major thrombotic event, fatal stroke). Cost of disability (rehabilitation and long-term care).

(b) Time horizon 10 years.

(c) 2003 GBP. Costs incorporated are: Intervention 1: anticoagulation clinic attendances (staff, equipment, consumables and overheads).Intervention 2: cost of training (2 or 3 sessions), machine (also for patients not continuing with the intervention; the cost was amortised over 3 years), consumables, assessment (15 minute long and carried out by a nurse) and telephone contact for advice specific to PSM. Anticoagulation clinic attendances for patients reverting to usual care.

(d) Time horizon 1 year.

Both studies concluded that patient self monitoring is not cost-effective.

12.1.1.3 Evidence statements

Clinical

In seven studies with 2419 people it is unlikely there is a clinically important difference in recurrent VTE between people in the self monitoring or self management group and people in the usual care group (VERY LOW QUALITY).

In 21 studies with 5726 people it is unlikely there is a clinically important difference in major bleeding between people in the self monitoring or self management group and people in the usual care group (LOW QUALITY).

In 12 studies with 2240 people it is very uncertain whether there is a clinically important difference in minor bleeding between people in the self monitoring or self management group and people in the usual care group (VERY LOW QUALITY).

In seven studies with 1549 people it is unlikely there is a difference of clinical importance in the percentage of time that INR was in range in people in the self management group compared to people in the usual care group (VERY LOW QUALITY).

In eight studies with 3158 people there was a decrease in the percentage of time INR was in range in people in the usual self monitoring compared to people in the usual group, but this decrease is not clinically important (LOW QUALITY).

For INR measurements out of range, there were 15 studies with approximately 4320 patients which could not be pooled; the difference ranged from 3% to 38% (VERY LOW QUALITY).

Economic

Patient self management is not likely to be cost-effective compared to usual care as the incremental cost per QALY gained was above the £20,000/QALY threshold in two studies included (£33,000/QALY in one study and £ 64,000/QALY in the other study). In the probabilistic sensitivity analyses patient self management was cost-effective in less than half of the simulations.

This evidence has minor limitations and direct applicability.

12.2 Recommendations and link to evidence

Recommendations	31. Do not routinely offer self-management or self-monitoring of INR to patients who have had DVT or PE and are having treatment with a VKA.
Relative values of different outcomes	The GDG considered recurrent VTE and major bleeding as the most important outcomes for this recommendation. The percentage of time INR was in range was considered an important outcome for patients as it might be a useful marker of effectiveness of the intervention.
Trade off between clinical benefits and harms	The balance between a decrease in recurrent VTE and occurrence of major bleeding was considered. Evidence shows that it is highly uncertain whether there is a difference between self monitoring or self management and usual care in the number of people experiencing a major bleeding event or recurrent VTE.
Economic considerations	Patient self management is not likely to be cost -effective compared to usual care when the cost of the machine and training is included among the costs paid for by the NHS. The incremental cost per QALY gained was above the £20,000/QALY threshold in two studies included (£33,000/QALY in one study and £ 64,000/QALY in the other study). In the probabilistic sensitivity analyses patient self-management was cost-effective in less than half of the simulations.
Quality of evidence	Overall, the quality of evidence for all the outcomes was low to very low. There was a lack of description of randomisation generation and allocation concealment methods. There were many variations in the population, intervention, comparison and outcomes between the studies included in this review. However, a large study published recently [157] has had an impact on the direction of outcome of the meta- analyses. This contributed 2922 participants to a total of 7645 included in the review. Although this study did have its limitations, the quality was considered better than many earlier studies which also had important limitations. The evidence was mostly from an indirect population, i.e. patients with atrial fibrillation or patients with a mechanical heart valve who received VKA for the prevention of stroke. None of the studies included only VTE patients. Despite this, there should be no difference in how self management or self monitoring would work for people taking VKAs. Nevertheless, the GDG was concerned that bleeding rates may be higher in the population studied; these patients were older than an average VTE patient, and at higher risk of bleeding. There were also variations in how major bleeding was reported; six studies did not define major bleeding at all. In addition, thromboembolic events were reported (which was not an outcome of interest for this review) by most studies instead of recurrent VTE, and this limited the evidence available for a key outcome. The interpretation of the evidence was complicated by the heterogeneity of intervention between studies; different types of education and training were provided and frequency of monitoring varied between studies. Due to the large variations between studies, the more conservative random effects analysis was used for all outcomes. However, fixed effect models were also used for sensitivity testing to ensure that this approach would not have an impact on the decision making since it gives more weight to smaller studies which are potentially lower quality. Sensitivity analyses excluding high risk of bias data, such as unpublished data from Kaatz2001 were also conducted. There were no important impacts on the

Recommendations	31. Do not routinely offer self-management or self-monitoring of INR to patients who have had DVT or PE and are having treatment with a VKA.
	key outcomes considered, except for the minor bleeding outcomes (the RR changed from 1.02 [0.76, 1.36] to 0.89 [0.47, 1.68] for the self monitoring subgroup when Katz was excluded). The minor bleeding outcome was also poorly defined or did not have an a priori definition in most studies. The quality of evidence for this outcome is very low. Statistical heterogeneity was also observed, and pre-specified subgroup analyses for minor bleeding and percentage of time within INR range were carried out. There was no evidence that these subgroups were different. The setting of the studies and the countries in which the studies were carried out was considered during the development of this recommendation. The economic evidence has minor limitations and direct applicability.
Other considerations	The evidence showed that there is no important difference between INR self monitoring or self management and usual care. These options are not cost effective for the NHS. Apart from the provision of machines, there are also costs involved in the training and ongoing support required. Therefore, self monitoring or management were not recommended as routine. The GDG agreed that INR self monitoring or management would currently not be appropriate for the majority of patients receiving anticoagulation. In addition to self monitoring or self management not being cost effective, it was highlighted that there is currently no widely agreed way for providing an education programme for patients wishing to self monitor or self manage, and not everyone is a suitable candidate for self monitoring or self management. There are serious implications to the safe and effective use of VKAs if patients start self monitoring or self manage without adequate training and knowledge of how to do it safely. The GDG discussed and acknowledged that for some patients who are on anticoagulation indefinitely, INR self monitoring or self management may mean less interruptions in their daily living through reduction in monitoring visits, and they may consider this to have an impact on their quality of life. Therefore, some patients may wish to purchase their own monitoring equipment with the agreement of their health professionals. If a patient wishes to use a point of care device they should discuss the implications with their anticoagulation service. Please see patient information chapter and recommendation 28 and 29 about education for patients on VKA. Link to the following clinical guidelines: CG36 Atrial Fibrillation, 2006. Recommendation 59 of this guideline refers to anticoagulation self monitoring for patients with atrial fibrillation. This recommendation was based on evidence from a direct population. Patient Experience (expected publication February 2012), which offers important guidance for involving patients in decision making.

13 Investigations for cancer in VTE patients

13.1 Introduction

Historically cancer and VTE have been considered as two unconnected disease entities or diagnoses. However, the inherent relationship between these two pathologies has become increasingly clear. During the process of malignant transformation, tumours produce several proteins, such as tissue factor, which enable the tumour cells to invade and metastasize. Tissue factor simultaneously activates the coagulation cascade leading to VTE. It is well established that there is a threefold increased risk of recurrent VTE with cancer, both solid and lympho-proliferative[235]. The occurrence of cancer related VTE leads to a poorer overall prognosis with a 12% one year survival from the diagnosis of VTE[115,209].

A proportion of patients with VTE have no underlying cause identified and the VTE is referred to as idiopathic or unprovoked. More commonly, the term is loosely used to refer to cases of VTE where the cause is not immediately apparent, and therefore these cases have the potential for a more specific diagnosis to be made. Apparent unprovoked VTE also heralds a significant increase in the risk of cancer within the first 1-2 years, with a standardised incidence ratio of 4.4 in a Swedish population-based study involving nearly 62 000 patients over 18 years [18]. This is equivalent to approximately 11% of all patients.

Recent studies have shown there are differences in the optimum form of VTE management strategy between patients with cancer and those without cancer (unprovoked VTE), which result in significant reductions in VTE recurrence rates.

In this context, it is important to clarify that a number of published studies and guidelines on the topic of investigating patients presenting with a VTE for cancer have used the phrase ‘cancer screening’. ‘Cancer screening’ in this context refers to the investigation of patients who present symptomatically with a DVT and/or PE to determine whether the VTE could be related to a previously undetected cancer; therefore this guideline shall refer to this as “investigations for cancer”.

An accurate diagnosis of the type of VTE and in particular whether it is a cancer associated VTE is critical to the optimal management of a patient. The search for the underlying cause of VTE in a symptomatic patient is distinctly different from the usual usage of the term ’screening’, where ‘screening‘ is used to denote the conduct of tests in asymptomatic individuals in the general population, for example mammography for breast cancer, or occult blood testing and flexible sigmoidoscopy for colorectal cancer.

The main body of literature related to investigating patients with a VTE for cancer pre-dates our understanding of the significant differences in management required for these patients. The literature has often focused on the early diagnosis of the underlying cancer to improve overall survival rather than, as discussed above, its ability to optimise VTE management, and minimise morbidity due to recurrent VTEs. Similarly, some guidelines do not recommend investigating patients for an underlying cancer due to a focus on mortality, rather than its significant impact on the type of treatment, VTE recurrence and morbidity.

Current clinical practice, in regards to the extent of investigations to determine the underlying cause of VTE, is variable. In this chapter, we aim to consider whether investigations to look for an underlying (and previously undetected) cancer in patients with symptomatic VTE are clinically and cost effective. If cancers are identified through this process, this could have an impact on the patient’s mortality and morbidity through the implementation of appropriate VTE treatment, and early treatment of the cancer and cost-effective.

13.1.1 Do investigations for cancer in patients with spontaneous VTE (DVT or PE) improve patient outcomes (morbidity and mortality)?

See clinical evidence tables in Appendix E.15 and Economic evidence tables in Appendix F.

13.1.1.1 Clinical evidence

Only one RCT was found.[192] This study assessed the value of intensive investigations for cancer in addition to routine history, examination, blood tests and chest x-rays in patients with a first episode of an unprovoked VTE. Out of 1020 patients referred, 339 met the inclusion criteria (see note (c) below). The excluded patients had a known malignancy and obvious predisposing cause including recent trauma, surgery, and or immobility. A further 138 were excluded for a variety of reasons; 65 patients had previous VTEs, and importantly 32 (9-10%) were found to have cancer based on routine investigations (history/physical examination focussing on signs and symptoms of malignant disease, full blood count, liver function tests, calcium, urinalysis and chest x-ray). Therefore, 201 patients were randomised between further investigations for cancer (including CT scans, ultrasound scans mammography and tumour markers), and no further tests.

Table 73: Intensive investigations for cancer vs. routine tests – Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Cancer related mortality at 2 years [(a)] [192]	1	RCT	Serious limitations [(b)]	No serious inconsistency	No serious indirectness [(c)]	Serious imprecision [(d)]
Early stage cancer detection (T1 & T2) [192]	1	RCT	Serious limitations [(b)]	No serious inconsistency	No serious indirectness [(c)]	Serious imprecision [(d)]
Delay in cancer diagnosis (months) [192]	1	RCT	Serious limitations [(b)]	No serious inconsistency	Serious indirectness [(c)]	No serious imprecision [(e)]
Sensitivity of intensive cancer investigations [192]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness [(c)]	Serious imprecision [(d)]

(a) Defined as death due to a malignant disease itself, or death due to complications of diagnostic or surgical procedures performed to diagnose or treat.

(b) The sample size was smaller than required. The reasons for stopping early were 1) There were issues with the recruitment of patients because there were not enough centres consenting for participation due to ethical concerns about the design of the study (Zelen's design –patients in the control group were not be aware that they were participating in the study 2) The increasing tendency among physicians in the participating hospitals to initiate screening for cancer in the control.

(c) The study recruited a selective group of patient, only 201 patients randomised, out of 1020 screened. To be included, patients had to have a first episode of VTE, without any identifiable risk factors. Pre-randomisation, all patients had baseline tests and physical examination – 9.4% of patients (32/339) of patients was found to have cancer, were not randomised. However the recommendations were made specifically for the group as identified and therefore there is no indirectness of evidence. It is unclear whether participation in this study affected whether patients in the control arm have investigations for cancers conducted earlier or later than in real clinical practice.

(d) The CIs were wide and crossed the thresholds considered as important harms and benefits (MID).

(e) No further downgrading for imprecision, because of the large & potentially clinically important difference in average time of delay.

Table 74: Intensive investigations for cancer – Clinical summary of findings

Outcome	Intensive investigations	Routine investigations	Effect measure	Absolute effect	Quality
Cancer related mortality at 2 years	2/99 (2%)	4/102(3.9%)	RR 0.52 (0.10 to 2.75)	19 fewer per 1000 (from 35 fewer to 69 more)	LOW
Early stage cancer detection (T1 and T2)	9/14 (64%)	2/10 (20%))	3.21 [0.88, 11.79]	442 more per 1000 (from 24 fewer to 1000 more)	LOW
Delay in cancer diagnosis (months)	1.0 (in 14 patients)	11.6 (in 10 patients)	Not applicable	10.6 months longer for routine investigations , p<0.001 reported in papers	LOW
Sensitivity of the intensive cancer investigation strategy	13/14 detected out of 99 patients	Not applicable	Sensitivity; 92.85%, (CI 66-100%)	72 cases missed per 1000 cancer patients (from 440 missed to none missed)	LOW

13.1.1.2 Economic evidence

Four studies were found on investigation for cancer in DVT patients. Three studies[19,20,173] were excluded as no details of results were provided (for example costs were not reported and ICERs were reported only for few strategies).

We included one study[53] which compared different strategies to investigate for cancer. Although this study tried to answer a different question (what is the most cost-effective test sequence), we could estimate the incremental cost-effectiveness of conducting cancer investigations vs. no investigations as the cost and effectiveness of the combinations of tests were calculated incrementally from the 'no investigations' strategy. Results are summarised and reported as ranges (lowest – highest) in the economic evidence profile below (Table 75 and Table 76). See also economic evidence tables in Appendix F.

Table 75: Intensive testing for cancer – Economic study characteristics

Study	Limitations	Applicability	Other comments
Di Nisio 2005[53]	Potentially serious limitations (a)	Partially applicable (b)	Within-trial analysis with modelled extrapolation based on a RCT[192] included in our clinical review (0).

(a) Breakdown of costs and other data input in the model (for example treatment success, probability of having a specific type of cancer) were not explicitly reported. Discounting was not reported. Effectiveness but not cost of cancer treatment was taken into account. Cost-effectiveness of investigations might depend on the absolute risk of cancer; this was not appropriately accounted for in the sensitivity analysis. The authors identified the following limitations: the RCT on which the analysis was based was stopped prematurely and included only 201 patients. The difference in mortality between patients who received investigations and patients who did not receive any was not significant. The sensitivity and specificity of the tests were really uncertain as they were based on few patients. Several assumptions on life expectancy in patients with cancer were made. Patients with thrombophilia were included in the RCT. Patients under the age of 25 were excluded. The risk due to radiation was not included in the analysis.

(b) Study conducted in the Netherlands. QALYs were not estimated in the original study but the NCGC assumed people surviving had a utility equal to that of the general population in the UK (0.86).[126]

Table 76: Intensive testing for cancer – Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Di Nisio 2005[53]	Range: 7,555-44,128[(a)]	Range: 3.44-32.68 [(b)]	Range: 724-5,517	Not reported[(c)]

(a) 2001 Euro were converted into GBP using the purchasing power parities[177]. Cost components included are: tests, subsequent evaluations (for example specialist consultations, biopsies) including false positives. Cost of initial treatment of VTE, basic tests and assessment and follow-up were not taken into account. Cost of cancer treatment was excluded.

(b) The incremental life years gained reported in the studies were adjusted by the average utility of the UK general population (0.86).[126]

(c) Sensitivity analyses were conducted on the cost-effectiveness of different strategies and are not applicable to the comparison between investigations vs. no investigations. Cost-effectiveness of investigations might depend on the absolute risk of cancer; this was not appropriately accounted for in the sensitivity analysis.

The study compared different strategies for investigating for cancer including abdominal/pelvic CT or abdominal/pelvic ultrasound scan, alone or in combination with other tests (mammography, sputum cytology, tumour markers, FOBT, and colonoscopy). Antigen tests with and without PSA and FOBT were also compared to ultrasound scan and CT strategies.

Strategies with abdominal/pelvic CT were associated with a low number of false positives. Adding mammography, sputum cytology and tumour markers was the most effective strategy in terms of the number needed to screen (7.6 vs. 9.9 with CT only); however the number of false positives (patients evaluated further for a benign condition) was high (26 false positive cases). This problem was observed in all the strategies based on tumour markers (26 false positive cases in all the strategies including tumour markers).

Based on these clinical results, a decision model was built to compare cost and life years gained for each strategy. In this analysis also CT thorax was included even if this was not part of the original SOMIT study. The calculation of life years gained was not entirely clear as it did not match the data reported on the number of cases detected and the number of false positives. Therefore the conclusions are based on the analysis of costs and the number of true positives and false positives.

The least costly strategies are those including antigen tests but they are also the least effective as they have a low number of cases detected (maximum 6) and a relatively high number of false positives (from 23 up to 43). All the strategies including ultrasound scan are dominated (more costly and less effective) by CT strategies. Among the CT strategies, CT thorax and CT + markers are associated with the highest number of cases detected (13); however there are also many cases of false positives in the CT + markers strategy (26 to 40) and a high cost associated with CT thorax. Considering the balance between these factors, the strategy based on abdominal/pelvic CT + mammography + sputum cytology seemed to provide the best value-for-money.

13.1.1.3 Evidence statements

Clinical

One study in 201 people showed that there may be a decrease which is potentially clinically important in cancer related mortality between the intensive testing for cancer group and the routine testing group at 2 years (LOW QUALITY EVIDENCE).

Among the 24 patients with cancer detected out of 201 participants, the evidence showed that there was an increase which maybe of clinical important in the intensive testing for cancer group compared to the routine testing group in the number of early stage cancer detected (Stage T1 and T2). There is an improvement in time to cancer detection which is likely to be clinically important in the group with intensive testing for cancer, compared to those undergoing routine tests (LOW QUALITY EVIDENCE).

One study involving 99 patients showed that sensitivity for intensive cancer screening was 92.9%. This means that 7 out of a 100 people with the cancer will be missed with this strategy. This implies that this test can be considered for ruling out cancer in people with unprovoked VTE (LOW QUALITY EVIDENCE).

Economic

Further investigation for cancer in patients with idiopathic DVT is cost-effective when the cost of cancer treatment is not considered. The most cost-effective test strategy includes abdominal/pelvic CT, mammography and sputum cytology. Adopting a strategy which involves either ultrasound scan, antigen tests, tumour markers, FOBT, PSA or colonoscopy is not cost-effective. This evidence has potentially serious limitations and partial applicability.

13.2 Recommendations and link to evidence

Recommendations	**32. Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:** • **a physical examination (guided by the patient's full history) *and*** • **a chest X-ray *and*** • **blood tests (full blood count, serum calcium and liver function tests) *and*** • **urinalysis.**
Relative values of different outcomes	Number of cancers detected (incidence) was considered the most important outcome because early detection of cancer and treatment may improve survival rates and reduce morbidity in patients. It can also enable patients to make better decisions about based on the availability of information on their underlying diagnosis. Therefore, the sensitivity and specificity of investigations were important outcomes.
Trade off between clinical benefits and harms	The potential benefit of detecting cancer early and initiating treatment (reducing potential mortality and morbidity), and of instituting the optimal form and duration of anticoagulation (reducing potential morbidity for complication of anticoagulation treatment or recurrence) was considered against the potential harm from using these tests. These tests apart from chest x-rays and serum Calcium, form part of the routine assessment of all patients with VTE to determine severity, and safety of anticoagulation. Therefore, there is little additional harm associated with their use for clarifying the cause of the VTE, where this may be an underlying cancer. The radiation dose associated with chest x-ray is also minimal, and is done in all patients with a suspected PE, and a proportion with a DVT where there is an associated suspicion of PE. Clinicians have to be aware that VTE can be the presenting symptom of cancer and they should consider cancer while conducting the examination and tests. These combinations of tests have been shown to detect cancer in about 10% of patients with a first episode of unprovoked VTE with no prior cancer diagnosis. Therefore the GDG recommend that these tests should be offered to all patients with unprovoked VTE. Patients who have a suspected cancer based on these tests should be directed to the appropriate local cancer diagnosis and care pathways.

Recommendations	**32. Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:** • **a physical examination (guided by the patient's full history) *and*** • **a chest X-ray *and*** • **blood tests (full blood count, serum calcium and liver function tests) *and*** • **urinalysis.**
Economic considerations	Offering baseline tests such as physical examination, history, chest X-ray and blood tests is associated with some costs. However, given the high prevalence of cancer in the screened population, offering these tests have been shown to detect about half of all cancers.
Quality of evidence	There was no evidence comparing performing the baseline tests vs no tests. However one RCT showed that this combination of tests detect cancer in about 10% of patients with first episode unprovoked VTE. Please see the "Quality of Evidence" section in the recommendation for intensive investigations for further details.
Other considerations	Physical examination, medical history documentation and baselines tests should be conducted and interpreted with a focus on the possibility that a patient with unprovoked VTE (no obvious risk factor identified) may have an underlying cancer. This should be performed in all patients, as there are few disadvantages and cancer can be effectively detected in up to half of all patients presenting with VTE and having an underlying cancer.

Recommendations	**33. Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation (see recommendation 32).**
Relative values of different outcomes	Number of cancers detected (incidence) was considered the most important outcome because early detection of cancer and treatment may affect survival rates and reduce morbidity in patients. All cause mortality is also an important outcome, but the GDG recognised its limitation as an outcome measure in this situation, given the heterogeneity of primary cancer sites, cancer specific treatment and survival rates.
Trade off between clinical benefits and harms	The potential benefit of detecting cancer early and initiating cancer treatment (therefore reducing potential mortality and morbidity), and of instituting the optimal form and duration of anticoagulation that is appropriate for patients with cancer related VTE was considered against potential harm from routine investigation for cancer. The clearest benefit is in the change in pharmacological management and duration of anticoagulation for VTE, in those whose underlying cancer is diagnosed, leading to a significant reduction in VTE recurrence rates. Early diagnosis of underlying cancer may lead to diagnosis at an earlier curative stage and improvement in cancer related mortality. The GDG considered that the patient might simply but significantly want to

Recommendations	**33. Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation (see recommendation 32).**
	know given the 1 in 10 risk of cancer, as this would have a significant impact on personal decision for their own future. Harms include exposing more patients to the radiation associated with CT scans and mammography. The radiation from abdomino-pelvic CT scans would be associated with an increased incidence of cancer of (1-2 per 10,000), for every 1000 cancers diagnosed in this group. Patients and their families are likely to experience psychological distress from knowing that they have a 1 in 10 risk of an underlying cancer and from undergoing the investigative procedures. However investigations with a 93% sensitivity (the chance of not detecting that a person has cancer is 7in 100) would provide a degree of reassurance. The GDG decided the potential harms and additional costs may be outweighed by the number of cancers detected and its impact on the management of the VTE. The GDG considered that the patient might want to undergo further investigation knowing that the risk of cancer is 1 in 10 patients.
Economic considerations	Further assessment for cancer in patients with an idiopathic VTE is cost-effective. Some strategies are more cost-effective than others. In particular, using abdomino-pelvic CT is cost-effective. Adding mammography and sputum cytology is cost-effective as more cases are detected with a small number of false positives. The GDG noted that the increase in radiation exposure was not factored into the cost effectiveness analysis conducted in the study reviewed. Other tests such as ultrasound scan, tumour markers, faecal occult blood test (FOBT), prostate specific antigen, thorax CT, and antigen tests are not cost-effective as the small increase in the number of cases detected does not justify the high rate of false positive cases and the associated increase in costs.
Quality of evidence	Only 201 out of 1020 of patients initially referred for first documented VTE without apparent risk factors were included in the study. The study was terminated early because of difficulty recruiting the patients into the study and an increased number of intensive testing for cancer given to the control group. The evidence quality was low; there were considerable uncertainty about the estimates obtained because of the small sample size and study limitations. It is possible that there may be a clinically important reduction in overall cancer related mortality, but the CIs were wide. The sensitivity of the strategy investigated in the study was high, but there were serious imprecision. The reduction in delay of cancer diagnosis by about 10 months for the intensive testing group may be clinically important, but direct outcomes on patient mortality and morbidity are more useful indicators on its impact on patient outcome. Since only a small proportion of screened patients qualify for the study, this also suggests that the data is applicable to only a selective group of patient: patients with unprovoked VTE. The economic evidence was based on the study included in the clinical review. Therefore, the same potential serious limitations reported for the clinical

Recommendations	**33. Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation (see recommendation 32).**
	evidence were applicable. In addition, breakdown of costs and other data input in the model were not explicitly reported; effectiveness but not cost of cancer treatment was taken into account; the risk due to radiation was not included in the analysis and partial applicability (patients with thrombophilia were included in the RCT while patients under the age of 25 were excluded; analysis not conducted from the UK NHS perspective).
Other considerations	While considering the evidence, the GDG noted the following points: • **The incidence of cancer:** 9.4% of patients with first episode unprovoked VTE who underwent the baseline routine tests had cancer detected. Over the course of 2 years, an additional 24/201(11.9%) developed cancer. These overall rates of an underlying cancer in patients with an unproved VTE are consistent with data from multiple large published registry studies (see below). • **Who will most likely benefit from intensive investigations for cancer:** Patients with an apparently unprovoked VTE over the age of 40 years are most likely to benefit. There were no cancers detected in the above study, in patients less than 40 years of age, and only one person less than 50 years had an underlying cancer. This is consistent with epidemiological data on cancer incidence in general, and in particular a UK cohort study [164] showed that the risk of cancer is lower for VTE patients who are less than 40 years old, but the incidence increased significantly in patients who were greater than 60 years old. The percentage of patients with cancer increased from 0.25% in those aged 35-39 years to 1.1% in those aged 40-44 years, and increased further in those aged up to 70-74 years before dropping slightly for older people. The study reported a cancer incidence of 2.3% within 1 month to 12 months of all VTE diagnoses (1334/59,534) based on data from the information and statistics division of the National Health Service in Scotland for 1982-2000. Given that idiopathic VTE represents about 20% of cases, the projected cancer incidence of 11.5% is in keeping with the study reviewed, and this data is applicable to this recommendation • **Limitations in the economic evaluation:** The long term costs and burden of cancer due to radiation from CT scans were not included in the cost-effectiveness analysis. • **Impact on the NHS: The recommendation is limited to patients with an** apparently unprovoked VTE (as in the study), which represents only 20% of patients with a VTE, and further restricting it to patients over the age of 40years, in whom a cancer has not been detected by routine investigations, will significantly limit the workload and capacity impact on the NHS, of this recommendation while potentially maximising benefit. • **Patient preferences.** The threshold of underlying risk of cancer at which patient with an unprovoked VTE would prefer to be immediately investigated, in view of the impact of a cancer diagnosis on patients in general, independent of any beneficial impact on survival is unknown. However, the clinical use and acceptability of investigations with OGD and colonoscopy in patients with anaemia, and/or other investigations in patients with weight loss for an underlying cancer, suggest that a 10% risk associated with VTE is a threshold at which patients would want to be investigated. This issue in general is being addressed by the Discovery Initiative in cancer, but not in VTE specifically.

Recommendations	**33. Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation (see recommendation 32).**
	The GDG agreed that the group where more intensive tests to detect cancer is most appropriate are patients over 40 years old, with an apparently unprovoked VTE. The most effective and cost-effective investigations for cancer that balance sensitivity and specificity includes abdominal/pelvic CT, mammography and sputum cytology. Studies have suggested that among patients with VTE, a large number of the cancers most commonly found are those in the abdomen and pelvic areas (ovary, pancreas, liver, kidney colon) [107]. Adopting an intensive testing strategy which involves ultrasound scans, antigen tests, tumour markers, FOBT, PSA or colonoscopy increases false positives without significant increases in sensitivity. Although the evidence of cost-effectiveness for further investigation of cancer in the study showed that a combination of pelvic abdominal CT, sputum cytology and mammography for women, the GDG thought that sputum cytology should not be recommended routinely for this purpose. They had taken into consideration that NICE guideline for "treatment and diagnosis of lung cancer" (CG121) which recommended "Sputum cytology is rarely indicated and should be reserved for patients with centrally placed nodules or masses who are unable to tolerate bronchoscopy or other invasive tests". In addition, testing for cancer in patients with apparently idiopathic VTE is also justifiable simply based on the significant difference in VTE management of patient with cancer compared to those without cancer, both in terms of choice of anticoagulants and duration of anticoagulation, and the significant impact of this on VTE recurrence rates. This guideline recommends that cancer patients with a VTE should be treated with a LMWH for 6 month, instead of a VKA for 3 months which should be reserved for patents without an underlying cancer. Hence, establishing whether a patient with VTE has an underlying cancer is critical to the appropriate management of their VTE. Testing for cancer in patients with VTE will also conform to national policies such, as the National Awareness and Early Diagnosis Initiative (NAEDI) in cancer. In deciding whether to offer additional investigations to detect an underlying cancer, the individual circumstances of patients such as co-morbidities and their preferences, must be considered. The GDG have prioritised this recommendation as a key priority for implementation as they considered that it has a high impact on outcomes that are important to patients, a high impact on reducing variation in care and outcomes, leads to a more efficient use of NHS resources, promotes patient choice and means patients reach critical points in the care pathway more quickly.

Summary of research recommendations

The GDG recommended the following research questions:

5. **A confirmatory trial to assess the impact of additional investigations for cancer in patients with VTE (CT abdo/pelvis, sputum cytology, and mammography) in patients with a first episode of apparently unprovoked VTE, on treatment for VTE, on morbidity due to VTE recurrence and overall survival, with patients diagnosed with a cancer associated VTEs receiving LMWH for at least 6months instead of a VKA for 3 months.**

The current guidance for additional investigations beyond routine baseline tests, are persuasive based on the robust evidence of benefit from LMWH versus VKA in patients with cancer associated VTE.[138] However, in the study reviewed,[192] support is provided for additional investigations for cancer diagnosis, but all patients in this study irrespective of cancer diagnosis received VKA based anti-coagulation, as it pre-dated the CLOT trail. A study addressing the impact of additional investigations for cancer, on VTE management based on the CLOT study, is required to enable future guidance in this area to be more definitive.

6. **Identification of novel non-invasive alternative strategies for the diagnosis of underlying cancers without the radiation risk associated with CT scanning and mammography**

The aim of this research recommendation is to enable diagnosis of underlying cancers in patients with a VTE, without the need for abdomino-pelvic CT scans and/or mammography. Both of these tests require significant resources, and are associated with radiation exposure. The development of simple non-invasive tests could potentially provide an alternative with lower risks and costs.

7. **Assessment of patient views on the threshold risk for occult cancer, at which they would prefer to be investigated with a 1-2 per 10,000 lifetime risk of cancer, irrespective of the impact of diagnosis on survival**

This qualitative study would inform the evidence base for conducting investigations for cancer in patients with VTE, and add to the data from the RCT included in the study reviewed.[192] Demonstration of a significant impact on morbidity, from a patient perspective, due to investigations for cancer and on survival benefit would enable the recommendation to screen to be strengthened, and would have a profound effect on the management of these patients. Patients views are at the heart of decisions on management, data on the perceived threshold of risk acceptable to patients, due to investigations for early diagnosis, will help inform not only this recommendation, but also others associated with cancer diagnosis. Finally, the main risk associated with the screening investigations is radiation exposure. Development of non-invasive radiation free alternatives would further shift the clinical risk-benefit balance in favour of screening.

14Thrombophilia testing

14.1Introduction

Thrombophilia is an acquired or inherited predisposition to venous thrombosis. The only important acquired thrombophilia is the presence of antiphospholipid antibodies (detected as a lupus anticoagulant or as antibodies against cardiolipin or β_2-glycoprotein I). Heritable thrombophilias include deficiencies in one of the three natural anticoagulants; antithrombin, protein C and protein S, which have been linked with familial venous thrombosis for many years. More recently the factor V Leiden mutation and the prothrombin G20210 mutation have been shown to carry an increased risk of venous thrombosis.

Thrombophilia testing is defined by the GDG as testing for the heritable thrombophilias described above but may also include testing for antiphospholipid antibodies, which can be performed at specialist centres through a panel of diagnostic blood tests. Thrombophilia testing might have clinical utility for a patient with VTE if: 1) initiation and intensity of anticoagulant therapy differed in those with a positive test, 2) the finding of a thrombophilia increased the risk of recurrence such that long-term rather than short term anticoagulation was favoured, or3) action can be taken to prevent VTE in a family member.

14.1.1 What is the effectiveness of thrombophilia testing in preventing recurrence of a venous thromboembolic event?

14.1.1.1Clinical evidence

No clinical evidence was identified.

14.1.1.2Economic evidence

One Health Technology Assessment[229] was included in this review that examined the cost-effectiveness of thrombophilia testing. This is summarised in the economic evidence profile (see Table 77 and Table 78). See also the full study evidence tables in Appendix F.

Some studies were identified but excluded for this question because they were less applicable than the included study[229]:

Eckman et al (2002)[61]: partially applicable (study from the USA)

Marchetti et al (2001)[156]: partially applicable (study from Italy)

Marchetti et al (2000)[155]: partially applicable (study from Italy)

Auerbach et al (2004)[7]: partially applicable (study from the USA)

Clark et al (2002)[37]: partially applicable (QALYs not estimated; population was pregnant women)

Smith et al (2008)[230]: partially applicable (study from the USA)

Wu et al (2005)[269]: wrong population (not on patients with VTE but high risk patients).

Some of the studies that were excluded for the question on patients with VTE were included in the review on thrombophilia testing in first degree relatives (see 14.3.1.2).

Table 77: Thrombophilia testing vs no testing - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Simpson et al (2009)[229]	Directly applicable	Potentially serious limitations [(a)]	Decision analytic model based on a patient-based discrete event simulation. Thrombophilia testing includes test for lupus anticoagulant, factor V Leiden and prothrombinG20210A, anticardiolipin antibody, factor V Leiden homozygous, deficiency in either antithrombin, protein C or protein S. When thrombophilia was detected, the most cost-effective treatment strategy was used. Cost-effectiveness of different duration of treatment with warfarin was based on gender, age and thrombophilia classification.

(a) Utility estimates based on expert opinion or small studies. Uncertainty not explored fully as prevalence of thrombophilia types was not altered in the PSA. Prevalence of thrombophilia was taken from unselected patients, including non-idiopathic DVT. Sensitivity and specificity of tests for each thrombophilia type were not used. Only warfarin was evaluated as an intervention to prevent recurrent VTE.

Table 78: Thrombophilia testing – Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Simpson et al (2009)[229]	(a, b)	(c)	(d)	- Testing in patients with PE is always cost-effective. - One-way SA: when it was assumed that untreated patients have the same outcomes as patients treated after VTE results did not change. - Threshold analysis: the cost of thrombophilia testing was varied; it showed no particular impact of this variable on the results. - PSA: risk of recurrence explained over 50% of the variation in the results.

(a) Thrombophilia testing is always more costly than no testing.

(b) Costs included were thrombophilia testing, treatment with warfarin (various duration), fatal and non-fatal PE, recurrent DVT, PTS, fatal haemorrhage, non-fatal intracranial haemorrhage and non-fatal non-intracranial haemorrhage.

(c) Thrombophilia testing generates more QALYs than no testing except for women aged 60 years or older.

(d) ICER is above £20,000/QALY in 50 years old women (£20,286/QALY). Testing is dominated in women above the age of 60. For the other subgroups the ICER is below £20,000/QALY.

A systematic review was conducted to inform the HTA model[229] but no studies comparing testing for thrombophilia vs no testing were available, as confirmed by our clinical review. As a consequence, the model was not based on a systematic review of studies on thrombophilia testing but on discrete parameters such as thrombophilia prevalence, relative risk of VTE recurrence for different types of thrombophilia, effectiveness of treatment at preventing recurrences, which were obtained from different sources retrieved with extensive literature searches. The GDG discussed the methods and conclusions of the included study and they concluded that the economic analysis by Simpson et al. (2009)[229] has potentially serious limitations. In fact, the authors accepted that factor V Leiden does not make any difference to the risk of VTE recurrence. They identified certain patients who were better off on long-term anticoagulation (for example men aged less than 39 years with a previous PE)

whether they had factor V Leiden or not but investigated a strategy of only giving long-term anticoagulation to those who had factor V Leiden. The study concluded that testing for factor V Leiden was cost effective but this was be due to the fact that these patients received the correct treatment, which could have been given to all patients with no testing at all.

14.1.1.3 Evidence statements

Clinical — No clinical evidence was identified.

Economic — Based on a published HTA,[229] testing in patients with PE is cost-effective. Testing in patients with DVT is cost-effective in men younger than 70 years and women younger than 50 years but there is great uncertainty around these results. However, after discussion the GDG concluded that treating on the basis of other factors, without testing for thrombophilia, would be effective and therefore cost-effective.

This evidence is directly applicable but it has potentially serious limitations.

14.2 Recommendations and link to evidence

Recommendations	34. Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment.
Relative values of different outcomes	The rate of VTE recurrence was considered the most important outcome for this recommendation. The other important and relevant outcomes were: VTE related mortality, symptomatic/asymptomatic PE, symptomatic DVT, psychological impact, patient preference or patient views.
Trade off between clinical benefits and harms	There was no evidence on whether thrombophilia testing impacts on any of the outcomes identified among patients who continue anticoagulant treatment. The GDG considered that information obtained from thrombophilia testing would not affect the treatment plan for this population. There may also be a psychological impact associated with thrombophilia testing that could lead to stress and anxiety in patients.
Economic considerations	A UK economic model showed that thrombophilia testing is cost-effective in patients with PE in men younger than 70 years and women younger than 50 years who had a DVT. However, the testing strategy was cost-effective because of its implications on the management of the patient (therefore the patient would be prescribed anticoagulation). If the patient is already receiving long-term anticoagulation, thrombophilia testing becomes unnecessary and increases costs with no additional benefits.
Quality of evidence	No clinical evidence was found. The economic evidence was directly applicable but has potentially serious limitations. The GDG discussed this at length, taking into consideration the clinical benefits and harms of thrombophilia testing in patients (see 'Other considerations' below).
Other considerations	In the absence of evidence of the clinical effectiveness of thrombophilia testing in reducing recurrent VTE, the GDG considered whether thrombophilia testing may lead to any changes in management that would improve patient outcomes. If a decision is made to continue anticoagulation treatment, it is unnecessary to offer thrombophilia testing as the results would not alter management. The decision to continue anticoagulation should be made with reference to:

Recommendations	**34. Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment.**
	whether a first episode of VTE was provoked or unprovoked; if the first VTE was a PE as recurrences are more likely to be in the form of a second PE; other risk factors for VTE recurrence (such as male sex, raised D-dimer and PTS); whether the person has chronic thromboembolic pulmonary hypertension (see section 7.4 Duration of anticoagulation). Only once the decision to stop anticoagulation treatment is made should thrombophilia testing be considered in selected patients (see Recommendations 36 and 37).

Recommendations	**35. Consider testing for antiphospholipid antibodies in patients who have had unprovoked DVT or PE if it is planned to stop anticoagulation treatment.**
Relative values of different outcomes	The rate of VTE recurrence was considered the most important outcome for this recommendation. The other important and relevant outcomes were: VTE related mortality, symptomatic/asymptomatic PE, symptomatic DVT, psychological impact, patient preference or patient views.
Trade off between clinical benefits and harms	Antiphospholipid antibodies (detected as a lupus anticoagulant or as antibodies to cardiolipin or β2glycoprotein I) increase the risk of VTE recurrence. The identification of antiphospholipid antibodies may influence the perceived balance of risks and benefits (prevention of VTE recurrence vs risk of major bleeding with treatment) and overall support long-term anticoagulant therapy. There may be a psychological impact associated with thrombophilia testing that could lead to stress and anxiety in patients. Patient views on whether they wish to be tested, and on long-term anticoagulation, should be taken into account.
Economic considerations	The cost-effectiveness of extended anticoagulation treatment depends on the risk of VTE recurrence (see section 7.4). If the patient is already receiving long-term anticoagulation, thrombophilia testing becomes cost-effective when deciding the future management of the patient (for example to stop or continue anticoagulation). Restricting the number of tests to offer patients could be cost-effective if a single test (such as antiphospholipid antibodies test) is able to accurately identify patients who need long-term anticoagulation. This is based only on GDG consensus and no evidence was found on the cost-effectiveness of antiphospholipid antibodies testing.
Quality of evidence	No clinical or economic evidence was found. The GDG discussed this at length, taking into consideration the clinical benefits and harms of thrombophilia testing in patients (see 'Other considerations' below).
Other considerations	Antiphospholipid syndrome is relatively uncommon; however the probability of a positive test will be increased in people with an unprovoked VTE. If there is a plan to stop anticoagulation treatment in these patients then a test for antiphospholipid antibodies could inform the balance of risks and benefits involved in the decision. Exclusion of a lupus anticoagulant is problematic whilst on warfarin and testing may have to take place after brief discontinuation of anticoagulation. The GDG considered that the additional risk associated with antiphospholipid

Recommendations	35. Consider testing for antiphospholipid antibodies in patients who have had unprovoked DVT or PE if it is planned to stop anticoagulation treatment.
	syndrome was not that great. Testing should therefore only be considered if, after assessment of the other risk factors in an individual patient with an unprovoked VTE, the plan is to stop anticoagulation. Patients continuing on anticoagulation treatment for other reasons do not require testing as it will not alter management. If there is an absolute contraindication to continuing anticoagulation or the patient does not wish to continue with anticoagulation even if they tested positive then testing would not be required. Hence only if the result could alter management should testing be performed. For patients with a family history of VTE testing for heritable thrombophilias should be considered (see recommendation 37).

Recommendations	36. Consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment.
Relative values of different outcomes	The rate of VTE recurrence was considered the most important outcome. The other important and relevant outcomes were: VTE related mortality, symptomatic/asymptomatic PE, symptomatic DVT, psychological impact, patient preference or patient views.
Trade off between clinical benefits and harms	The finding of a natural anticoagulant (antithrombin, protein C, or protein S) deficiency in a young patient with unprovoked VTE and a strong family history of unprovoked VTE might increase the risk of recurrence and make long-term anticoagulation favourable. There may be a psychological impact associated with thrombophilia testing that could lead to stress and anxiety in patients. Patient views on whether they wish to be tested should be taken into account.
Economic considerations	The cost-effectiveness of extended anticoagulation treatment depends on the risk of VTE recurrence ((see 7.4.2.2). If the patient is already receiving long-term anticoagulation, thrombophilia testing becomes cost-effective when deciding the management of the patient (for example to stop or continue anticoagulation). This is based only on GDG considerations and no evidence was found for this group of patients and intervention.
Quality of evidence	No clinical or economic evidence was found. The GDG discussed this at length, taking into consideration the clinical benefits and harms of thrombophilia testing in patients (see below).
Other considerations	The GDG considered that the test for hereditary thrombophilia should be offered to people of any age with unprovoked VTE who have a first degree relative with VTE so that it reduces the risk of any patient who may have a hereditary thrombophilia being missed. The GDG considered that testing for heritable thrombophilia in unselected VTE patients may not usefully predict recurrence. However, it cannot be excluded that the finding of a natural anticoagulant (antithrombin, protein C, or protein S) deficiency in a patient with unprovoked VTE and a family history of VTE

Recommendations	**36. Consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment.**
	might increase the risk of recurrence and make long-term anticoagulation favourable[142]. The GDG also considered that in unselected patients having a first degree relative with VTE does not help to identify patients with hereditary thrombophilia[252]. However, penetrant mutations in thrombosis prone families will more likely be found where there is a thrombosis at a young age which the GDG agreed to be less than 50 years. If testing patients with unprovoked VTE and a family history of venous thrombosis, it would be reasonable to restrict testing to the natural anticoagulants (protein C, protein S and antithrombin) as factor V Leiden and the prothrombin mutation do not increase the risk of recurrence to a clinically significant extent.

Recommendations	**37. Do not offer thrombophilia testing to patients who have had provoked DVT or PE.**
Relative values of different outcomes	Rate of VTE recurrence was considered the most important outcome. The other important and relevant outcomes were: VTE related mortality, symptomatic/asymptomatic PE, symptomatic DVT, psychological impact, patient preference or patient views.
Trade off between clinical benefits and harms	There was no evidence on whether thrombophilia testing impacts on any of the outcomes identified among patients with provoked VTE. The GDG considered that information obtained from thrombophilia testing would not affect the treatment plan for this population and these patients are unlikely to have thrombophilia. There may also be a psychological impact associated with thrombophilia testing that could lead to stress and anxiety in patients.
Economic considerations	Providing thrombophilia testing would unnecessarily increase costs when the episode of VTE was provoked by other factors and the patient is unlikely to have thrombophilia. This is based on GDG consensus and not on economic evidence.
Quality of evidence	No clinical or economic evidence was found. The GDG discussed this at length, taking into consideration the clinical benefits and harms of thrombophilia testing in patients (see below).
Other considerations	Patients who have a provoked VTE are at less risk of recurrence and will be given short-term anticoagulation as standard treatment whether they have thrombophilia or not. Testing therefore has no utility as it does not change patient management.

14.3 Thrombophilia testing for first degree relatives of people who had thromboembolic disease and thrombophilia

Thrombophilia testing for first degree relatives of people who have had thromboembolic disease and thrombophilia could theoretically lead to the reduction of VTE risk, if there are suitable interventions which can be applied to the relatives who are affected. However a family history of VTE increases a person's risk of having a VTE whether they have a thrombophilia or not. These relatives would receive thromboprophylaxis in at risk situations; such as surgery, trauma or immobilisation.

A further consideration is whether the finding of a thrombophilia in a female relative is useful regarding advice about the combined oral contraceptive pill (CoCP), hormone replacement therapy (HRT) or pregnancy and whether a positive test would affect the treatment options.

14.3.1 Does thrombophilia testing improve the outcomes of first degree relatives of people who have had thromboembolic disease and thrombophilia?

See economic evidence table in Appendix F.

14.3.1.1 Clinical evidence

No clinical evidence was identified.

14.3.1.2 Economic evidence

Two studies[230,269] were included that assessed the cost-effectiveness of thrombophilia screening in people with a family history of VTE or thrombophilia. These are summarised in the economic evidence profile below (Table 79 and Table 80). See also the full study evidence tables in Appendix F.

One study[37] was excluded because the population, pregnant women, was not included in the scope.

Table 79: Thrombophilia testing vs. no testing - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Smith 2008[230]	Potentially serious limitations[(a)]	Partially applicable[(b)]	Decision model. Time horizon was 30 years. The population was asymptomatic female relatives of factor V Leiden carriers prior to starting oral contraceptive pills. Thrombophilia testing was the test for factor V Leiden. Strategies compared were no screening, screening and counselling for oral contraceptive pill, screening with counselling and anticoagulation in high risk period, screening with counselling and long-term anticoagulation. Clinical parameters were obtained from the literature.
Wu 2005[269]	Potentially serious limitation [(c)]	Partially applicable[(d)]	Decision model. Thrombophilia screening comprised of testing for factor V Leiden, prothrombin G20210A, deficiencies of antithrombin, protein C and protein S, lupus anticoagulants and anticardiolipin antibodies. No thromboprophylaxis was included. Population was women with previous

Study	Limitations	Applicability	Other Comments
			personal and/or family history of VTE a) prior to prescribing combined oral contraceptives b) prior to prescribing hormone replacement therapy. Other strategies were analysed (screening at the onset of pregnancy, screening prior to major elective orthopaedic surgery) but were excluded from our evidence as they were respectively outside the scope and already covered by a previous guideline (CG92). Universal screening (anyone including people with no personal or family history of VTE) was included in the study but not reported here as it was not the population included in the review question. Assumptions: overall sensitivity and specificity of screening tests is 80%.

(a) Baseline mortality used in the model was not described/not incorporated; distributions used in the PSA are not the most appropriate ones. Strategies were not compared to the 'anticoagulation with no screening' strategy. Some disutilities were based on the number of days lost due to hospitalisation.

(b) The population is not exactly the population included in the guideline question: relatives of factor V Leiden carriers, instead of relatives of individuals who had thromboembolic disease (prevalence might be lower, unclear if this parameter has been tested). Study conducted in the USA.

(c) Time- horizon and discounting not reported. Sensitivity analysis not conducted on selective screening (only universal screening). Source of funding not reported.

(d) No estimation of QALYs. Patients with a personal history of VTE were grouped together with patients with a family history of VTE. Prevalence of thrombophilia was based on general population and was not specific to people with personal or family history of VTE.

Table 80: Thrombophilia testing vs. no testing – Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Women prior to prescribing combined oral contraceptives				
Smith 2008[230]	(a)	(b)	(c)	One-way SA: results were sensitive to cost of prophylaxis, VTE relative risk reduction with prophylaxis. Threshold analysis: all the screening strategies would be less costly than no screening if the costs of screening tests were <$77 (£49). PSA: uniform distributions were used for costs and probabilities, triangular distributions for relative risks, beta distributions for utilities, gamma distribution for disutilities. Probability cost-effective at a $20,000/QALY threshold: no screening: 10% screening no prophylaxis: 13% screening + high-risk prophylaxis: 74 %

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
				screening + long-term prophylaxis: 3% Similar probabilities for higher acceptability thresholds (up to $100,000/QALY).
Wu 2005[269]	7[(d)]	Mean clinical complications prevented per patient: 0.00009	£77,778 per clinical complication prevented	Sensitivity analysis was conducted only on the universal screening model (all patients, not only patients with previous family/personal history of VTE).
Women prior to prescribing hormone replacement therapy				
Wu 2005[269]	3[(e)]	Mean clinical complications prevented per patient: 0.0014	£2,143 per clinical complication prevented	Sensitivity analysis was conducted only on the universal screening model (all patients, not only patients with previous family/personal history of VTE).

(a) Screening strategies with no prophylaxis or prophylaxis in high risk events were less costly than no screening strategies. Screening with long-term prophylaxis has an incremental cost of £1,737 compared to no screening. Costs included were screening and counselling, DVT and PE treatment, minor and major bleed, death, postphlebitic syndrome, LMWH treatment for 21 months (high-risk prophylaxis strategy) or 15 years (long-term prophylaxis strategy).

(b) Screening strategies yield higher QALYs. Incremental QALYs were 0.014 with no prophylaxis strategy, 0.97 with high-risk prophylaxis strategy, and 0.101 with long-term prophylaxis. Some disutilities were based on the number of days lost due to hospitalisation.

(c) Screening with no prophylaxis was less costly and more effective than no screening. The ICERs of the screening strategies were: £92/QALY for high-risk prophylaxis vs no prophylaxis, and £436,000/QALY for long-term prophylaxis vs high-risk prophylaxis.

(d) Costs incorporated were cost of screening, management of DVT and PE, cost of combined oral contraceptive.

(e) Costs incorporated were cost of screening, management of DVT and PE, cost of hormone replacement therapy.

The studies included in our review[230,269] did not completely answer the review question because the population and the strategies incorporated in the analyses did not exactly match those that were of interest to the GDG. In fact, none of the studies assessed the cost-effectiveness of screening compared to the management of the patient based on the family history. In women with a family history of VTE, a strategy including counselling prior to prescribing combined oral contraceptives or hormone replacement therapy with no thrombophilia screening might be cost-effective. The study by Smith et al. (2008)[230] concluded that screening is cost-effective, however the population was relatives of factor V Leiden carriers instead of people with a family history of VTE. In the population included in the study, the prevalence of thrombophilia might be higher compared to the population of our review question for whom screening might be less cost-effective as fewer cases would be detected.

14.3.1.3 Evidence statements

Clinical — No clinical evidence was identified.

Economic — Thrombophilia testing could be cost-effective in relatives of people with thrombophilia. This evidence has potentially serious limitations and partial applicability. There was no evidence on the cost-effectiveness of managing people with a family history of VTE on the basis of their family history only.

14.4 Recommendations and link to evidence

Recommendations	**38. Do not routinely offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia.**
Relative values of different outcomes	The GDG considered a reduction in VTE (symptomatic/asymptomatic PE, symptomatic DVT) in the relative to be the most important outcome. Other outcomes that were considered were: VTE related mortality, psychological impact, patient preference/patient views and pick up rates.
Trade off between clinical benefits and harms	Thrombophilia testing of first degree relatives might lead to the reduction of VTE if there are suitable interventions, that they would not otherwise receive, which can be applied to those relatives who are affected. There is a psychological impact associated with thrombophilia testing that could lead to stress and anxiety in patients.
Economic considerations	Thrombophilia testing could be cost-effective in relatives of people with thrombophilia only if there are suitable interventions which can be applied to those who are affected. This evidence has potentially serious limitations and partial applicability. There was no evidence for the cost-effectiveness of managing people with a family history of VTE on the basis of their family history only. This strategy could be more cost-effective than providing testing. For example In women with a family history of VTE, a strategy including counselling prior to prescribing combined oral contraceptives or hormone replacement therapy with no thrombophilia screening might be cost-effective.
Quality of evidence	No clinical evidence was found. The GDG discussed this at length, taking into consideration the different groups of relatives that may require thrombophilia testing (see below). The economic evidence has potentially serious limitations and partial applicability.
Other considerations	The GDG considered whether thrombophilia testing should be offered to first degree relatives of patients with VTE and known thrombophilia. The GDG decided that the tests are not routinely required, because it does not alter the decision of whether to give these people thromboprophylaxis as it is routinely given to all first degree relatives of those who have had thromboembolic disease. Thus, thrombophilia testing does not alter decision making in terms of thromboprophylaxis (see CG92). The GDG discussed females of childbearing age with regard to the combined oral contraceptive pill (COCP); and older women considering the use of hormone replacement therapy (HRT). For females planning to start the COCP, testing for a specific thrombophilia may be helpful, although a negative thrombophilia result does not exclude an increased risk of venous thrombosis as the risk of venous thrombosis can be increased in unaffected family members as well as in those affected. In many instances an alternative effective contraceptive is acceptable and thrombophilia testing is unnecessary. Women considering HRT who have a first degree relative who has had a VTE are at higher risk than the general population and therefore oral HRT would not normally be recommended. Therefore, thrombophilia testing would not affect the treatment options. Transdermal HRT appears not to increase the risk of VTE and can therefore be considered in these women either without thrombophilia testing. This recommendation is worded differently from other recommendations in this guideline which do not recommend thrombophilia testing. The GDG

Recommendations	38. Do not routinely offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia.
	worded this as “do not routinely” (instead of “do not”) after taking into the consideration that although the test is usually not useful, there are rare circumstances where this test could be of benefit, particularly in issues related to pregnancy (which is not within the scope of the guideline). Therefore the GDG do not wish to be prescriptive in suggesting that this test should not be offered at all for this situation. Issues related to pregnancy are not covered in this guideline and specialist advice should be sought if thrombophilia testing is to be considered in these situations.

14.5 Research recommendations

8. **Do antithrombin, protein C or protein S deficiencies increase the risk of recurrence to a clinically significant degree when anticoagulation is stopped as compared to those patients with venous thrombosis who do not have thrombophilia?**

Why this is important - It is known that factor V Leiden and the prothrombin mutation only minimally increase the risk of recurrence when anticoagulation is stopped. If antithrombin, protein C or protein S deficiencies increase the risk of recurrence to a clinically significant degree then testing would have utility in those patients stopping anticoagulation on clinical grounds. A prospective cohort study/RCT is required to find out whether patients with antithrombin, protein C or protein S deficiencies have an increased risk of recurrence when anticoagulation is stopped. All patients stopping anticoagulation on clinical grounds would have a thrombophilia screen. Doctors and patients would be blinded to the results and all patients would be given advice about prophylaxis in high risk situations and monitored for recurrence. The primary outcome would be VTE recurrence rates in those with thrombophilia as compared to those without.

15 References

1 Urokinase pulmonary embolism trial. Phase 1 results: a cooperative study. Journal of the American Medical Association. 1970; 214(12):2163-2172. *(Guideline Ref ID ANON1970)*

2 Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Annals of Internal Medicine. Sezione di Medicina Interna e Cardiovascolare, Dipartimento di Medicina Interna, Universita di Perugia, Via Enrico Dal Pozzo, 06123 Perugia, Italy. agnellig@unipg.it 2003; 139(1):19-25. *(Guideline Ref ID AGNELLI2003)*

3 Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. New England Journal of Medicine. Dipartimento di Medicina Interna, Universita di Perugia, Italy. agnellig@unipg.it 2001; 345(3):165-169. *(Guideline Ref ID AGNELLI2001A)*

4 Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, Hirsch A et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. Journal of the American Medical Association. 2007; 298(23):2743-2753. *(Guideline Ref ID ANDERSON2007)*

5 Anoop P, Chappell P, Kulkarni S, Shirley JA. Evaluation of an immunoturbidimetric D-dimer assay and pretest probability score for suspected venous thromboembolism in a district hospital setting. Hematology. 2009; 14(5):305-310. *(Guideline Ref ID ANOOP2009)*

6 Arnesen H, Heilo A, Jakobsen E, Ly B, Skaga E. A prospective study of streptokinase and heparin in the treatment of deep vein thrombosis. Acta Medica Scandinavica. 1978; 203(6):457-463. *(Guideline Ref ID ARNESEN1978)*

7 Auerbach AD, Sanders GD, Hambleton J. Cost-effectiveness of testing for hypercoagulability and effects on treatment strategies in patients with deep vein thrombosis. American Journal of Medicine. 2004; 116(12):816-828. *(Guideline Ref ID AUERBACH2004)*

8 Aujesky D, Hayoz D, Yersin B, Perrier A, Barghouth G, Schnyder P et al. Exclusion of pulmonary embolism using C-reactive protein and D-dimer. A prospective comparison. Thrombosis & Haemostasis. 2003; 90(6):1198-1203. *(Guideline Ref ID AUJESKY2003)*

9 Aujesky D, Hughes R, Jimenez D. Short-term prognosis of pulmonary embolism. Journal of Thrombosis & Haemostasis. 2009; 7 Suppl 1:318-321. *(Guideline Ref ID AUJESKY2009)*

10 Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-weight heparin for secondary prophylaxis of cancer-related venous thromboembolism. Thrombosis & Haemostasis. 2005; 93(3):592-599. *(Guideline Ref ID AUJESKY2005A)*

11 Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-weight heparin for treatment of pulmonary embolism. Chest. 2005; 128(3):1601-1610. *(Guideline Ref ID AUJESKY2005B)*

12 Aujesky D, Smith KJ, Roberts MS. Oral anticoagulation strategies after a first idiopathic venous thromboembolic event. American Journal of Medicine. 2005; 118(6):625-635. *(Guideline Ref ID AUJESKY2005)*

13 Avritscher EBC, Cantor SB, Shih Y-CT, Escalante CP, Rivera E, Elting LS. Cost-minimization analysis of low-molecular-weight heparin (daltepadn) compared to unfractionated heparin for inpatient treatment of cancer patients with deep venous thrombosis. Supportive Care in Cancer. 2004; 12(7):531-536. *(Guideline Ref ID AVRITSCHER2004)*

14 Aywak AA, Masesa JV. Comparison of sonography with venography in the diagnosis of deep venous thrombosis. East African Medical Journal. 2007; 84(7):304-311. *(Guideline Ref ID AYWAK2007)*

15 Baglin T, Douketis J, Tosetto A, Marcucci M, Cushman M, Kyrle P et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. Journal of Thrombosis & Haemostasis. 2010; 8(11):2436-2442. *(Guideline Ref ID BAGLIN2010)*

16 Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet. 2003; 362(9383):523-526. *(Guideline Ref ID BAGLIN2003)*

17 Barcellona D, Contu P, Marongiu F. A "two-step" educational approach for patients taking oral anticoagulants does not improve therapy control. Journal of Thrombosis & Thrombolysis. 2006; 22(3):185-190. *(Guideline Ref ID BARCELLONA2006)*

18 Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M. Venous thromboembolism and cancer. Lancet. 1998; 351(9109):1077-1080. *(Guideline Ref ID BARON1998)*

19 Barosi G, Marchetti M, Dazzi L, Quaglini S. Testing for occult cancer in patients with idiopathic deep vein thrombosis - a decision analysis. Thrombosis & Haemostasis. 1997; 78:1319-1326. *(Guideline Ref ID BAROSI1997)*

20 Barosi G, Marchetti M, Piovella F, Quaglini S. Cost-effectiveness of post-routine screening for an occult cancer in patients with idiopathic venous thromboembolism. Haematologica. 1995; 80(2 Suppl):S61-S65. *(Guideline Ref ID BAROSI1995)*

21 Beckman JA, Dunn K, Sasahara AA, Goldhaber SZ. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. Thrombosis & Haemostasis. 2003; 89(6):953-958. *(Guideline Ref ID BECKMAN2003)*

22 Bendayan P, Boccalon H. Cost-effectiveness of non-invasive tests including duplex scanning for diagnosis of deep vein thrombosis. Vasa - Journal of Vascular Diseases. 1991; 20:348-353. *(Guideline Ref ID BENDAYAN1991)*

23 Bernardi E, Camporese G, Buller HR, Siragusa S, Imberti D, Berchio A et al. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. Journal of the American Medical Association. 2008; 300(14):1653-1659. *(Guideline Ref ID BERNARDI2008)*

24 Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. Annals of Internal Medicine. 2000; 133(9):687-695. *(Guideline Ref ID BEYTH2000)*

25 Blum AG, Delfau F, Grignon B, Beurrier D, Chabot F, Claudon M et al. Spiral-computed tomography versus pulmonary angiography in the diagnosis of acute massive pulmonary embolism. American Journal of Cardiology. 1994; 74(1):96-98. *(Guideline Ref ID BLUM1994)*

26 Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet. 1997; 349(9054):759-762. *(Guideline Ref ID BRANDJES1997)*

27 Bratt G, Aberg W, Johansson M, Tornebohm E, Granqvist S, Lockner D. Two daily subcutaneous injections of fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis (DVT). Thrombosis & Haemostasis. 1990; 64(4):506-510. *(Guideline Ref ID BRATT1990)*

28 Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Annals of Internal Medicine. 2004; 140(11):867-873. *(Guideline Ref ID BULLER2004A)*

29 Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. New England Journal of Medicine. 2003; 349(18):1695-1702. *(Guideline Ref ID BULLER2003)*

30 Campbell IA, Bentley DP, Prescott RJ, Routledge PA, Shetty HG, Williamson IJ. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. British Medical Journal. Llandough Hospital, Llandough, Cardiff CF64 2XX. ian.campbell@cardiffandvale.wales.nhs.uk 2007; 334(7595):674. *(Guideline Ref ID CAMPBELL2007)*

31 Caro JJ, Getsios D, Caro I, O'Brien JA. Cost effectiveness of tinzaparin sodium versus unfractionated heparin in the treatment of proximal deep vein thrombosis. PharmacoEconomics. 2002; 20(9):593-602. *(Guideline Ref ID CARO2002)*

32 Cesarone MR. Three-month, outpatient, oral anticoagulant treatment in comparison with low-molecular-weight heparin in cancer patients. Circulation. 2003; 108(17 suppl):2875. *(Guideline Ref ID CESARONE2003)*

33 Chan KB, Man-Son-Hing M, Molnar FJ, Laupacis A. How well is the clinical importance of study results reported? An assessment of randomized controlled trials. CMAJ. 2001; 165(9):1197-1202. *(Guideline Ref ID CHAN2001)*

34 Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH, ASTH DVT Study Group. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis. Journal of Thrombosis & Thrombolysis. 2005; 19(3):173-181. *(Guideline Ref ID CHONG2005)*

35 Christensen TD, Maegaard M, Sorensen HT, Hjortdal VE, Hasenkam JM. Self-management versus conventional management of oral anticoagulant therapy: A randomized, controlled trial. European Journal of Internal Medicine. 2006; 17(4):260-266. *(Guideline Ref ID CHRISTENSEN2006)*

36 Christiansen F. Diagnostic imaging of acute pulmonary embolism. Acta Radiologica - Supplementum. 1997; 410:1-33. *(Guideline Ref ID CHRISTIANSEN1997A)*

37 Clark P, Twaddle S, Walker ID, Scott L, Greer IA. Cost-effectiveness of screening for the factor V leiden mutation in pregnant women. Lancet. 2002; 359(9321):1919-1920. *(Guideline Ref ID CLARK2002)*

38 Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thrombosis & Haemostasis. 2007; 98(4):756-764. *(Guideline Ref ID COHEN2007)*

39 Common HH, Seaman AJ, Rosch J, Porter JM, Dotter CT. Deep vein thrombosis treated with streptokinase or heparin. Follow-up of a randomized study. Angiology. 1976; 27(11):645-654. *(Guideline Ref ID COMMON1976)*

40 Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: A systematic review and economic modelling. Health Technology Assessment. 2007; 11(38):iii-50. *(Guideline Ref ID CONNOCK2007)*

41 Cromheecke ME, Levi M, Colly LP, de Mol BJ, Prins MH, Hutten BA et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. Lancet. 2000; 356(9224):97-102. *(Guideline Ref ID CROMHEECKE2000)*

42 D'Angelo A, D'Alessandro G, Tomassini L, Pittet JL, Dupuy G, Crippa L. Evaluation of a new rapid quantitative D-dimer assay in patients with clinically suspected deep vein thrombosis. Thrombosis & Haemostasis. 1996; 75(3):412-416. *(Guideline Ref ID DANGELO1996)*

43 Dalla-Volta S, Palla A, Santolicandro A, Giuntini C, Pengo V, Visioli O et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen activator Italian multicenter study 2. Journal of the American College of Cardiology. 1992; 20(3):520-526. *(Guideline Ref ID DALLAVOLTA1992)*

44 Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. World Journal of Surgery. 1996; 20(5):521-526. *(Guideline Ref ID DAS1996)*

45 Daskalopoulos ME, Daskalopoulou SS, Tzortzis E, Sfiridis P, Nikolaou A, Dimitroulis D et al. Long-term treatment of deep venous thrombosis with a low molecular weight heparin (tinzaparin): a prospective randomized trial. European Journal of Vascular & Endovascular Surgery. 2005; 29(6):638-650. *(Guideline Ref ID DASKALOPOULOS2005)*

46 Dauphin C, Legault B, Jaffeux P, Motreff P, Azarnoush K, Joly H et al. Comparison of INR stability between self-monitoring and standard laboratory method: preliminary results of a prospective study in 67 mechanical heart valve patients. Archives of Cardiovascular Diseases. Service de cardiologie et maladies vasculaires, hopital Gabriel-Montpied, CHU Clermont-Ferrand, place Henri-Dunant, BP 69, 63003 Clermont-Ferrand, France. cdauphin@chu-clermontferrand.fr 2008; 101(11-12):753-761. *(Guideline Ref ID DAUPHIN2008)*

47 de Lissovoy G, Yusen RD, Spiro TE, Krupski WC, Champion AH, Sorensen S, V. Cost for inpatient care of venous thrombosis: a trial of enoxaparin vs standard heparin. Archives of Internal Medicine. 2000; 160(20):3160-3165. *(Guideline Ref ID DELISSOVOY2000)*

48 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):409-415. *(Guideline Ref ID DECOUSUS1998)*

49 Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J et al. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clinical & Applied Thrombosis/Hemostasis. 2006; 12(4):389-396. *(Guideline Ref ID DEITCHER2006)*

50 Dempfle CE, Korte W, Schwab M, Zerback R, Huisman MV, CARDIM study group. Sensitivity and specificity of a quantitative point of care D-dimer assay using heparinized whole blood, in patients with clinically suspected deep vein thrombosis. Thrombosis & Haemostasis. 2006; 96(1):79-83. *(Guideline Ref ID DEMPFLE2006)*

51 Department of Health and Chief Medical Officer. Report of the independent expert working group on the prevention of venous thromboembolism in hospitalised patients. 2007 Available from: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_073950.pdf *(Guideline Ref ID DH2007)*

52 Di Nisio M, Rutjes AW, Buller HR. Combined use of clinical pretest probability and D-dimer test in cancer patients with clinically suspected deep venous thrombosis. Journal of Thrombosis & Haemostasis. 2006; 4(1):52-57. *(Guideline Ref ID DINISIO2006)*

53 Di Nisio N, Otten HM, Piccioli A, Lensing AW, Prandoni P, Buller HR et al. Decision analysis for cancer screening in idiopathic venous thromboembolism. Journal of Thrombosis & Haemostasis. 2005; 3(11):2391-2396. *(Guideline Ref ID DINISIO2005)*

54 Diamond S, Goldbweber R, Katz S. Use of D-dimer to aid in excluding deep venous thrombosis in ambulatory patients. American Journal of Surgery. 2005; 189(1):23-26. *(Guideline Ref ID DIAMOND2005)*

55 Dotter CT, Seaman AJ, Rosch J, Porter JM. Streptokinase and heparin in the treatment of pulmonary embolism: A randomized comparison. Vascular & Endovascular Surgery. 1979; 13(1):42-52. *(Guideline Ref ID DOTTER1979)*

56 Douketis J, Tosetto A, Marcucci M, Baglin T, Cosmi B, Cushman M et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. BMJ. 2011; 342:d813. *(Guideline Ref ID DOUKETIS2011)*

57 Douketis JD, Gu CS, Schulman S, Ghirarduzzi A, Pengo V, Prandoni P. The risk for fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism. Annals of Internal Medicine. 2007; 147(11):766-774. *(Guideline Ref ID DOUKETIS2007)*

58 Doyle NM, Ramirez MM, Mastrobattista J, Monga M, Wagner LK, Gardner MO. Diagnosis of pulmonary embolism: a cost-effectiveness analysis. American Journal of Obstetrics and Gynecology. 2004; 191(3):1019-1023. *(Guideline Ref ID DOYLE2004)*

59 Dranitsaris G, Vincent M, Crowther M. Dalteparin versus warfarin for the prevention of recurrent venous thromboembolic events in cancer patients: a pharmacoeconomic analysis. PharmacoEconomics. 2006; 24(6):593-607. *(Guideline Ref ID DRANITSARIS2006)*

60 Duriseti RS, Brandeau ML. Cost-effectiveness of strategies for diagnosing pulmonary embolism among emergency department patients presenting with undifferentiated symptoms. Annals of Emergency Medicine. 2010; 56(4):321-332. *(Guideline Ref ID DURISETI2010)*

61 Eckman MH, Singh SK, Erban JK, Kao G. Testing for Factor V Leiden in patients with pulmonary or venous thromboembolism: a cost effectiveness analysis. Medical Decision Making. 2002; 22(2):108-124. *(Guideline Ref ID ECKMAN2002)*

62 Eischer L, Gartner V, Schulman S, Kyrle PA, Eichinger S, AUREC-FVIII Investigators. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Annals of Hematology. Department of Internal Medicine I, Medical University of Vienna, Austria. 2009; 88(5):485-490. *(Guideline Ref ID EISCHER2009)*

63 Eitz T, Schenk S, Fritzsche D, Bairaktaris A, Wagner O, Koertke H et al. International normalized ratio self-management lowers the risk of thromboembolic events after prosthetic heart valve replacement. Annals of Thoracic Surgery. Department of Thoracic and Cardiovascular Surgery, Heart and Diabetes Center North Rhine-Westphalia,

Ruhr Universitat Bochum, Bad Oeynhausen, Germany. teitz@hdz-nrw.de 2008; 85(3):949-954. *(Guideline Ref ID EITZ2008)*

64 Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. European Journal of Vascular & Endovascular Surgery. 2002; 24(3):209-214. *(Guideline Ref ID ELSHARAWY2002)*

65 Estrada CA, Mansfield CJ, Heudebert GR. Cost-effective of low-molecular-weight heparin in the treatment of proximal deep vein thrombosis. Journal of General Internal Medicine. 2000; 15(2):108-115. *(Guideline Ref ID ESTRADA2000)*

66 Farraj RS. Anticoagulation period in idiopathic venous thromboembolism. How long is enough? Saudi Medical Journal. Department of Internal Medicine, King Hussein Medical Center, Amman 11180, Jordan. rfarraj@go.com.jo 2004; 25(7):848-851. *(Guideline Ref ID FARRAJ2004)*

67 Fasullo S, Scalzo S, Maringhini G, Ganci F, Cannizzaro S, Basile I et al. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. American Journal of the Medical Sciences. 2011; 341(1):33-39. *(Guideline Ref ID FASULLO2011)*

68 Fiessinger JN, Lopez-Fernandez M, Gatterer E, Granqvist S, Kher A, Olsson CG et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. Thrombosis & Haemostasis. 1996; 76(2):195-199. *(Guideline Ref ID FIESSINGER1996)*

69 Findik S, Erkan ML, Selcuk MB, Albayrak S, Atici AG, Doru F. Low-molecular-weight heparin versus unfractionated heparin in the treatment of patients with acute pulmonary thromboembolism. Respiration. 2002; 69(5):440-444. *(Guideline Ref ID FINDIK2002)*

70 Fitzmaurice DA, Murray ET, Gee KM, Allan TF, Hobbs FD. A randomised controlled trial of patient self management of oral anticoagulation treatment compared with primary care management. Journal of Clinical Pathology. 2002; 55(11):845-849. *(Guideline Ref ID FITZMAURICE2002)*

71 Fitzmaurice DA, Murray ET, McCahon D, Holder R, Raftery JP, Hussain S et al. Self management of oral anticoagulation: randomised trial. British Medical Journal. 2005; 331(7524):1057. *(Guideline Ref ID FITZMAURICE2005A)*

72 Fortes VB, Rollo HA, Fortes J, Sobreira MDL, Santos FC, Giannini M et al. Evaluation of a clinical prediction model by Wells et al. in the diagnosis of deep venous thrombosis of the lower limbs. Jornal Vascular Brasileiro. 2007; 6(1):7-16. *(Guideline Ref ID FORTES2007)*

73 Freyburger G, Trillaud H, Labrouche S, Gauthier P, Javorschi S, Bernard P et al. D-dimer strategy in thrombosis exclusion. A gold standard study in 100 patients suspected of deep venous thrombosis or pulmonary embolism: 8 DD methods compared. Thrombosis & Haemostasis. 1998; 79(2):32-37. *(Guideline Ref ID FREYBURGER1998)*

74 Gadisseur AP, Breukink-Engbers WG, van der Meer FJ, van den Besselaar AM, Sturk A, Rosendaal FR. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in the Netherlands: a randomized clinical trial. Archives of Internal Medicine. 2003; 163(21):2639-2646. *(Guideline Ref ID GADISSEUR2003)*

75 Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D et al. Self-monitoring and self-management of oral anticoagulation. Cochrane Database of Systematic Reviews. Department of Primary Health Care, University of Oxford, Old Road Campus, Old Road, Headington, Oxford, UK, OX3 7LF. 2010;(Issue 4):CD003839. *(Guideline Ref ID GARCIAALAMINO2010)*

76 Gardiner C, Williams K, Mackie IJ, Machin SJ, Cohen H. Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring. British Journal of Haematology. 2005; 128(2):242-247. *(Guideline Ref ID GARDINER2005A)*

77 Gibson NS, Schellong SM, Kheir DY, Beyer-Westendorf J, Gallus AS, McRae S et al. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. Journal of Thrombosis & Haemostasis. 2009; 7(12):2035-2041. *(Guideline Ref ID GIBSON2009)*

78 Goekoop RJ, Steeghs N, Niessen RWLM, Jonkers GJPM, Dik H, Castel A et al. Simple and safe exclusion of pulmonary embolism in outpatients using quantitative D-dimer and Wells' simplified decision rule. Thrombosis & Haemostasis. 2007; 97(1):146-150. *(Guideline Ref ID GOEKOOP2007)*

79 Goldhaber SZ, Haire WD, Feldstein ML, Miller M, Toltzis R, Smith JL et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet. 1993; 341(8844):507-511. *(Guideline Ref ID GOLDHABER1993)*

80 Goldhaber SZ, Meyerovitz MF, Green D, Vogelzang RL, Citrin P, Heit J et al. Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis. American Journal of Medicine. 1990; 88(3):235-240. *(Guideline Ref ID GOLDHABER1990B)*

81 Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999; 353(9162):1386-1389. *(Guideline Ref ID GOLDHABER1999)*

82 Gomez-Outes A, Rocha E, Martinez-Gonzalez J, Kakkar VV. Cost effectiveness of bemiparin sodium versus unfractionated heparin and oral anticoagulants in the acute and long-term treatment of deep vein thrombosis. PharmacoEconomics. 2006; 24(1):81-92. *(Guideline Ref ID GOMEZOUTES2006)*

83 Gonzalez-Fajardo JA, Arreba E, Castrodeza J, Perez JL, Fernandez L, Agundez I et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. Journal of Vascular Surgery. 1999; 30(2):283-292. *(Guideline Ref ID GONZALEZFAJARDO1999)*

84 Gonzalez-Fajardo JA, Martin-Pedrosa M, Castrodeza J, Tamames S, Vaquero-Puerta C. Effect of the anticoagulant therapy in the incidence of post-thrombotic syndrome and recurrent thromboembolism: Comparative study of enoxaparin versus coumarin. Journal of Vascular Surgery. 2008; 48(4):953-959. *(Guideline Ref ID GONZALEZFAJARDO2008)*

85 Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S et al. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technology Assessment. 2006; 10(15):1-168. *(Guideline Ref ID GOODACRE2006)*

86 Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low molecular-weight heparins compared with unfractionated heparin for treatment of acute deep vein thrombosis. A cost effectiveness analysis. Annals of Internal Medicine. 1999; 130(10):789-799. *(Guideline Ref ID GOULD1999)*

87 GRADE. Grading of Recommendations Assessment, Development and Evaluation working group. 2011. *(Guideline Ref ID GRADE2011)*

88 Gray HW, McKillop JH, Bessent RG, Fogelman I, Smith ML, Moran F. Lung scanning for pulmonary embolism: clinical and pulmonary angiographic correlations. Quarterly Journal of Medicine. 1990; 77(283):1135-1150. *(Guideline Ref ID GRAY1990)*

89 Gutte H, Mortensen J, Jensen CV, von der Recke P, Petersen CL, Kristoffersen US et al. Comparison of V/Q SPECT and planar V/Q lung scintigraphy in diagnosing acute pulmonary embolism. Nuclear Medicine Communications. 2010; 31(1):82-86. *(Guideline Ref ID GUTTE2010A)*

90 Hamann H. Prevention of recurrence after deep vein thrombosis - Oral anticoagulation or subcutaneous low molecular weight heparin? Vasomed. 1998; 10(3):133-136. *(Guideline Ref ID HAMANN1998)*

91 Heaton D, Pearce M. Low molecular weight versus unfractioned herapin: a clinical and economic appraisal. PharmacoEconomics. 1995; 8(2):91-99. *(Guideline Ref ID HEATON1995)*

92 Henschke C, I, Yankelevitz DF, Mateescu I, Whalen JP. Evaluation of competing tests for the diagnosis of pulmonary embolism and deep vein thrombosis, part I. Clinical Imaging. 1994; 18(4):241-247. *(Guideline Ref ID HENSCHKE1994)*

93 Hillner BE, Philbrick JT, Becker DM. Optimal management of suspected lower-extremity deep vein thrombosis. Archives of Internal Medicine. 1992; 152(1):165-175. *(Guideline Ref ID HILLNER1992)*

94 Horstkotte D, Piper C, Wiemer M. Optimal frequency of patient monitoring and intensity of oral anticoagulation therapy in valvular heart disease. Journal of Thrombosis & Thrombolysis. 1998; 5(3 Suppl 1):19-24. *(Guideline Ref ID HORSTKOTTE1998)*

95 House of Commons Health Committee. The prevention of venous thromboembolism in hospitalised patients: second report of Session 2004-05. (HC99). House of Commons, 2005 Available from: http://www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/99/99.pdf *(Guideline Ref ID HC2005)*

96 Hull R, Hirsh J, Sackett DL, Stoddart G. Cost effectiveness of clinical diagnosis, venography, and noninvasive testing in patients with symptomatic deep-vein thrombosis. New England Journal of Medicine. 1981; 304(26):1561-1567. *(Guideline Ref ID HULL1981)*

97 Hull RD, Feldstein W, Pineo GF, Raskob GE. Cost effectiveness of diagnosis of deep vein thrombosis in symptomatic patients. Thrombosis & Haemostasis. 1995; 74(1):189-196. *(Guideline Ref ID HULL1995)*

98 Hull RD, Feldstein W, Stein PD, Pineo GF. Cost-effectiveness of pulmonary embolism diagnosis. Archives of Internal Medicine. 1996; 156(1):68-72. *(Guideline Ref ID HULL1996)*

99 Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. American Journal of Medicine. 2006; 119(12):1062-1072. *(Guideline Ref ID HULL2006)*

100 Hull RD, Pineo GF, Raskob GE. The economic impact of treating deep vein thrombosis with low-molecular-weight heparin: outcome of therapy and health economy aspects. Haemostasis. 1998; 28(suppl 3):8-16. *(Guideline Ref ID HULL1998)*

101 Hull RD, Pineo GF, Stein PD, Mah AF, Butcher MS. Cost-effectiveness of currently accepted strategies for pulmonary embolism diagnosis. Seminars in Thrombosis & Hemostasis. 2001; 27(1):15-23. *(Guideline Ref ID HULL2001)*

102 Hull RD, Raskob GE, Brant RF, Pineo GF, Elliott G, Stein PD et al. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. American-Canadian Thrombosis Study Group. Archives of Internal Medicine. 2000; 160(2):229-236. *(Guideline Ref ID HULL2000A)*

103 Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. New England Journal of Medicine. 1992; 326(15):975-982. *(Guideline Ref ID HULL1992C)*

104 Hull RD, Raskob GE, Rosenbloom D, Pineo GF, Lerner RG, Gafni A et al. Treatment of proximal vein thrombosis with subcutaneous low-molecular-weight heparin vs intravenous heparin: an economic perspective. Archives of Internal Medicine. 1997; 157(3):289-294. *(Guideline Ref ID HULL1997A)*

105 Humphreys CW, Moores LK, Shorr AF. Cost-minimization analysis of two algorithms for diagnosing acute pulmonary embolism. Thrombosis Research. 2004; 113(5):275-282. *(Guideline Ref ID HUMPHREYS2004)*

106 Ilkhanipour K, Wolfson AB, Walker H, Cillo J, Rolniak S, Cockley P et al. Combining clinical risk with D-dimer testing to rule out deep vein thrombosis. Journal of Emergency Medicine. 2004; 27(3):233-239. *(Guideline Ref ID ILKHANIPOUR2004)*

107 Iodice S, Gandini S, Lohr M, Lowenfels AB, Maisonneuve P. Venous thromboembolic events and organ-specific occult cancers: a review and meta-analysis. Journal of Thrombosis & Haemostasis. 2008; 6(5):781-788. *(Guideline Ref ID IODICE2008)*

108 Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Controlled Clinical Trials. 1989; 10(4):407-415. *(Guideline Ref ID JAESCHKE1989)*

109 Jang T, Docherty M, Aubin C, Polites G. Resident-performed compression ultrasonography for the detection of proximal deep vein thrombosis: fast and accurate. Academic Emergency Medicine. Division of Emergency Medicine, Washington University School of Medicine, St. Louis, MO, USA. jangt@msnotes.wustl.edu 2004; 11(3):319-322. *(Guideline Ref ID JANG2004)*

110 Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes GM, Arriaga-Nava R, Valencia S, Rosado-Buzzo A et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. Journal of Thrombosis & Thrombolysis. 1995; 2(3):227-229. *(Guideline Ref ID JERJESSANCHEZ1995)*

111 Joint Formulary Committee. British National Formulary. (60). London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2010 *(Guideline Ref ID BNF2010)*

112 Jowett S, Bryan S, Murray E, McCahon D, Raftery J, Hobbs FDR et al. Patient self-management of anticoagulation therapy: a trial-based cost-effectiveness analysis. British Journal of Haematology.: Blackwell Publishing Ltd. 2006; 134(6):632-639. *(Guideline Ref ID JOWETT2006)*

113 Kaatz S, Elston-Lafata J, Gooldy S. Anticoagulation therapy home and office monitoring evaluation study. Journal of Thrombosis & Thrombolysis. 2001; 12:111. *(Guideline Ref ID KAATZ2001)*

114 Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. Journal of Thrombosis & Haemostasis. 2009; 7(5):879-883. *(Guideline Ref ID KAHN2009)*

115 Kakkar VV, Flanc C, Howe CT, O'Shea M, Flute PT. Treatment of deep vein thrombosis. A trial of heparin, streptokinase, and arvin. British Medical Journal. 1969; 1(5647):806-810. *(Guideline Ref ID KAKKAR1969A)*

116 Kakkar VV, Gebska M, Kadziola Z, Saba N, Carrasco P, Bemiparin Investigators. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. Thrombosis & Haemostasis. 2003; 89(4):674-680. *(Guideline Ref ID KAKKAR2003B)*

117 Kasper W, Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser KD et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. Journal of the American College of Cardiology. 1997; 30(5):1165-1171. *(Guideline Ref ID KASPER1997)*

118 Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. New England Journal of Medicine. McMaster University, Hamilton, Ont., Canada. 1999; 340(12):901-907. *(Guideline Ref ID KEARON1999)*

119 Kearon C, Ginsberg JS, Julian JA, Douketis J, Solymoss S, Ockelford P et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. Journal of the American Medical Association. 2006; 296(8):935-942. *(Guideline Ref ID KEARON2006)*

120 Khaira HS, Mann J. Plasma D-dimer measurement in patients with suspected DVT - a means of avoiding unnecessary venography. European Journal of Vascular & Endovascular Surgery. 1998; 15(3):235-238. *(Guideline Ref ID KHAIRA1998)*

121 Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. British Journal of Haematology. 2004; 126(4):557-564. *(Guideline Ref ID KHAN2004)*

122 Khorana AA, Streiff MB, Farge D, Mandala M, Debourdeau P, Cajfinger F et al. Venous thromboembolism prophylaxis and treatment in cancer: a consensus statement of major guidelines panels and call to action. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology. 2009; 27(29):4919-4926. *(Guideline Ref ID KHORANA2009)*

123 Kiil J, Carvalho A, Sakso P, Nielsen HO. Urokinase or heparin in the management of patients with deep vein thrombosis? Acta Chirurgica Scandinavica. 1981; 147(7):529-532. *(Guideline Ref ID KIIL1981)*

124 Kim HM, Kuntz KM, Cronan JJ. Optimal management strategy for use of compression US for deep venous thrombosis in symptomatic patients: a cost-effectiveness analysis. Academic Radiology. 2000; 7(2):67-76. *(Guideline Ref ID KIM2000)*

125 Kim HS, Patra A, Paxton BE, Khan J, Streiff MB. Adjunctive percutaneous mechanical thrombectomy for lower-extremity deep vein thrombosis: clinical and economic outcomes. Journal of Vascular & Interventional Radiology. 2006; 17(7):1099-1104. *(Guideline Ref ID KIM2006)*

126 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):736-741. *(Guideline Ref ID KIND1998)*

127 Kline JA, Nelson RD, Jackson RE, Courtney DM. Criteria for the safe use of D-dimer testing in emergency department patients with suspected pulmonary embolism: a multicenter US study. Annals of Emergency Medicine. 2002; 39(2):144-152. *(Guideline Ref ID KLINE2002)*

128 Kline JA, Runyon MS, Webb WB, Jones AE, Mitchell AM. Prospective study of the diagnostic accuracy of the simplify D-dimer assay for pulmonary embolism in emergency department patients. Chest. 2006; 129(6):1417-1423. *(Guideline Ref ID KLINE2006)*

129 Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, Management Strategies and Prognosis of Pulmonary Embolism. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. New England Journal of Medicine. 2002; 347(15):1143-1150. *(Guideline Ref ID KONSTANTINIDES2002)*

130 Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser K, Rauber K et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. Circulation. 1997; 96(3):882-888. *(Guideline Ref ID KONSTANTINIDES1997)*

131 Koopman MMW, Prandoni P, Piovella F, Ockelford PA, Brandjes DPM, van der Meer J et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. New England Journal of Medicine. 1996; 334(11):682-687. *(Guideline Ref ID KOOPMAN1996)*

132 Kortke H, Korfer R. International normalized ratio self-management after mechanical heart valve replacement: is an early start advantageous? Annals of Thoracic Surgery. 2001; 72(1):44-48. *(Guideline Ref ID KORTKE2001)*

133 Kremenski Z, V, Getov I. Pharmacoeconomic assessment of deep venous thrombosis. Farmaceutski Glasnik. 2001; 57(12):459-464. *(Guideline Ref ID KREMENSKI2001)*

134 Laporte S, Quenet S, Buchmuller-Cordier A, Reynaud J, Tardy-Poncet B, Tirion C et al. Compliance and stability of INR of two oral anticoagulants with different half-lives: A randomised trial. Thrombosis & Haemostasis. 2003; 89(3):458-467. *(Guideline Ref ID LAPORTE2003)*

135 Larcos G, Chi KK, Shiell A, Berry G. Suspected acute pulmonary emboli: cost-effectiveness of chest helical computed tomography versus a standard diagnostic algorithm incorporating ventilation-perfusion scintigraphy. Australian & New Zealand Journal of Medicine. 2000; 30(2):195-201. *(Guideline Ref ID LARCOS2000)*

136 Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Annals of Internal Medicine. 2006; 144(3):165-171. *(Guideline Ref ID LEGAL2006)*

137 Lebrun E, Maitre B, Grenier-Sennelier C, Katsahian S, Gouault-Heilmann M, Vasile N et al. Effect of D-dimer testing on the diagnostic strategy of suspected pulmonary embolism: an observational study of practice patterns and costs. European Radiology. 2000; 10(Suppl 3):S433-S434. *(Guideline Ref ID LEBRUN2000)*

138 Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. New England Journal of Medicine. 2003; 349(2):146-153. *(Guideline Ref ID LEE2003)*

139 Levi M. Epidemiology and management of bleeding in patients using vitamin K antagonists. [Review] [42 refs]. Journal of Thrombosis & Haemostasis. 2009; 7 Suppl 1:103-106. *(Guideline Ref ID LEVI2009)*

140 Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. New England Journal of Medicine. 1996; 334(11):677-681. *(Guideline Ref ID LEVINE1996)*

141 Levine M, Hirsh J, Weitz J, Cruickshank M, Neemeh J, Turpie AG et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. Chest. 1990; 98(6):1473-1479. *(Guideline Ref ID LEVINE1990A)*

142 Lijfering WM, Brouwer JL, Veeger NJ, Bank I, Coppens M, Middeldorp S et al. Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. Blood. 2009; 113(21):5314-5322. *(Guideline Ref ID LIJFERING2009)*

143 Lin PH, Zhou W, Dardik A, Mussa F, Kougias P, Hedayati N et al. Catheter-direct thrombolysis versus pharmacomechanical thrombectomy for treatment of symptomatic lower extremity deep venous thrombosis. American Journal of Surgery. 2006; 192(6):782-788. *(Guideline Ref ID LIN2006)*

144 Lindmarker P, Holmstrom M, Granqvist S, Johnsson H, Lockner D. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. Thrombosis & Haemostasis. 1994; 72(2):186-190. *(Guideline Ref ID LINDMARKER1994)*

145 Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Annals of Internal Medicine. 2003; 139(11):893-900. *(Guideline Ref ID LINKINS2003)*

146 Lloyd AC, Aitkin JA, Hoffmeyer UK, Kelso EJ, Wakerly EC, Barber ND. Economic evaluation of the use nadroparin in the treatment of deep-vein thrombosis in Switzerland. Annals of Pharmacotherapy. 1997; 31(7/8):842-846. *(Guideline Ref ID LLOYD1997)*

147 Lobo JL, Zorrilla V, Aizpuru F, Uresandi F, Garcia-Bragado F, Conget F et al. Clinical syndromes and clinical outcome in patients with pulmonary embolism: findings from the RIETE registry. Chest. 2006; 130(6):1817-1822. *(Guideline Ref ID LOBO2006)*

148 Lopaciuk S, Bielska-Falda H, Noszczyk W, Bielawiec M, Witkiewicz W, Filipecki S et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. Thrombosis & Haemostasis. 1999; 81(1):26-31. *(Guideline Ref ID LOPACIUK1999)*

149 Lopaciuk S, Meissner AJ, Filipecki S, Zawilska K, Sowier J, Ciesielski L et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. Thrombosis & Haemostasis. 1992; 68(1):14-18. *(Guideline Ref ID LOPACIUK1992)*

150 Lopez-Beret P, Orgaz A, Fontcuberta J, Doblas M, Martinez A, Lozano G et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. Journal of Vascular Surgery. 2001; 33(1):77-90. *(Guideline Ref ID LOPEZBERET2001)*

151 Luomanmaki K, Grankvist S, Hallert C, Jauro I, Ketola K, Kim HC et al. A multicentre comparison of once-daily subcutaneous dalteparin (low molecular weight heparin) and continuous intravenous heparin in the treatment of deep vein thrombosis. Journal of Internal Medicine. 1996; 240(2):85-92. *(Guideline Ref ID LUOMANMAKI1996)*

152 Ly B, Arnesen H, Eie H, Hol R. A controlled clinical trial of streptokinase and heparin in the treatment of major pulmonary embolism. Acta Medica Scandinavica. 1978; 203(6):465-470. *(Guideline Ref ID LY1978)*

153 Lyman GH, Khorana AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. Journal of Clinical Oncology. 2007; 25(34):5490-5505. *(Guideline Ref ID LYMAN2007)*

154 Marchetti M, Pistorio A, Barone M, Serafini S, Barosi G. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. American Journal of Medicine. 2001; 111(2):130-139. *(Guideline Ref ID MARCHETTI2001A)*

155 Marchetti M, Pistorio A, Barosi G. Extended anticoagulation for prevention of recurrent venous thromboembolism in carriers of factor V Leiden: Cost-effectiveness analysis. Thrombosis & Haemostasis. 2000; 84(5):752-757. *(Guideline Ref ID MARCHETTI2000)*

156 Marchetti M, Quaglini S, Barosi G. Cost-effectiveness of screening and extended anticoagulation for carriers of both factor V Leiden and prothrombin G20210A. Quarterly Journal of Medicine. 2001; 94(7):365-372. *(Guideline Ref ID MARCHETTI2001)*

157 Matchar DB, Jacobson A, Dolor R, Edson R, Uyeda L, Phibbs CS et al. Effect of home testing of international normalized ratio on clinical events. New England Journal of Medicine. 2010; 363(17):1608-1620. *(Guideline Ref ID MATCHAR2010)*

158 McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. Lancet. 2006; 368(9533):371-378. *(Guideline Ref ID MCRAE2006)*

159 Menendez-Jandula B, Souto JC, Oliver A, Montserrat I, Quintana M, Gich I et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. Annals of Internal Medicine. 2005; 142(1):1-10. *(Guideline Ref ID MENENDEZJANDULA2005)*

160 Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Annals of Internal Medicine. 2001; 134(3):191-202. *(Guideline Ref ID MERLI2001A)*

161 Meyer G, Brenot F, Pacouret G, Simonneau G, Gillet JK, Charbonnier B et al. Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. Thrombosis & Haemostasis. 1995; 74(6):1432-1435. *(Guideline Ref ID MEYER1995)*

162 Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Archives of Internal Medicine. 2002; 162(15):1729-1735. *(Guideline Ref ID MEYER2002)*

163 Michel BC, Seerden RJ, Rutten FFH, van Beek EJR, Buller HR. The cost-effectiveness of diagnostic strategies in patients with suspected pulmonary embolism. Health Economics. 1996; 5(4):307-318. *(Guideline Ref ID MICHEL1996)*

164 Murchison JT, Wylie L, Stockton DL. Excess risk of cancer in patients with primary venous thromboembolism: a national, population-based cohort study. British Journal of Cancer. 2004; 91(1):92-95. *(Guideline Ref ID MURCHISON2004)*

165 Murin S, Romano PS, White RH. Comparison of outcomes after hospitalization for deep venous thrombosis or pulmonary embolism. Thrombosis & Haemostasis. 2002; 88(3):407-414. *(Guideline Ref ID MURIN2002)*

166 National Institute for Clinical Excellence. Infection control. Prevention of healthcare-associated infections in primary and community care. (CG2)., 2003 Available from: http://guidance.nice.org.uk/CG2 *(Guideline Ref ID NICE2003)*

167 National Institute for Health and Clinical Excellence. The guidelines manual 2009. National Institute for Health and Clinical Excellence, 2009 Available from: http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/GuidelinesManual2009.jsp *(Guideline Ref ID NICE2009)*

168 National Institute of Clinical Excellence. Social value judgements: principles for the development of NICE guidance. 2008. *(Guideline Ref ID NICE2008)*

169 National Patient Safety Agency. Oral anticoagulant therapy: important information for patients. 2007. Available from: http://www.nrls.npsa.nhs.uk/resources/?entryid45=61777&p=11 *(Guideline Ref ID NPSA2007)*

170 National Patient Safety Agency. Reducing treatment dose errors with low molecular weight heparins. (RRR014)., 2010 Available from: http://www.nrls.npsa.nhs.uk/alerts/?entryid45=75208 *(Guideline Ref ID NPSA2010)*

171 Naz R, Naz S, Mehboob M, Achakzai A, Khalid GH. Diagnostic yield of color Doppler ultrasonography in deep vein thrombosis. Journal of the College of Physicians & Surgeons - Pakistan. 2005; 15(5):276-279. *(Guideline Ref ID NAZ2005A)*

172 Neale D, Tovey C, Vali A, Davies S, Myers K, Obiako M et al. Evaluation of the Simplify D-dimer assay as a screening test for the diagnosis of deep vein thrombosis in an emergency department. Emergency Medicine Journal. 2004; 21(6):663-666. *(Guideline Ref ID NEALE2004)*

173 Netzer P, Binek J, Hammer B, Schmassmann A. Utility of abdominal sonography in patients with idiopathic deep vein thrombosis. Journal of Clinical Ultrasound. 1999; 27(4):177-181. *(Guideline Ref ID NETZER1999)*

174 Nilsson T, Soderberg M, Lundqvist G, Cederlund K, Larsen F, Rasmussen E et al. A comparison of spiral computed tomography and latex agglutination D-dimer assay in acute pulmonary embolism using pulmonary arteriography as gold standard. Scandinavian Cardiovascular Journal. 2002; 36(6):373-377. *(Guideline Ref ID NILSSON2002)*

175 Ninet J, Bachet P, Prandoni P, Ruol A, Vigo M, Barret A et al. A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. Thrombosis & Haemostasis. 1991; 65(3):251-256. *(Guideline Ref ID NINET1991)*

176 Ohno Y, Higashino T, Takenaka D, Sugimoto K, Yoshikawa T, Kawai H et al. MR angiography with sensitivity encoding (SENSE) for suspected pulmonary embolism: comparison with MDCT and ventilation-perfusion scintigraphy. American Journal of Roentgenology. 2004; 183(1):91-98. *(Guideline Ref ID OHNO2004)*

177 Organisation for Economic Co-operation and Development. Purchasing Power Parities Data. 2011. [Last accessed: 19 September 2011] *(Guideline Ref ID OECD2011)*

178 Ost D, Khanna D, Shah R, Hall CS, Shah S, Lesser M et al. Impact of spiral computed tomography on the diagnosis of pulmonary embolism in a community hospital setting. Respiration. 2004; 71(5):450-457. *(Guideline Ref ID OST2004)*

179 Oudega R, Moons KG, Hoes AW. Ruling out deep venous thrombosis in primary care. A simple diagnostic algorithm including D-dimer testing. Thrombosis & Haemostasis. 2005; 94(1):200-205. *(Guideline Ref ID OUDEGA2005)*

180 Oudkerk M, van Beek EJR, Van Putten WLJ, Buller HR. Cost effectiveness analysis of various strategies in the diagnostic management of pulmonary embolism. Archives of Internal Medicine. 1993; 153(8):947-954. *(Guideline Ref ID OUDKERK1993)*

181 Ozbudak O, Erogullari I, Ogus C, Cilli A, Turkay M, Ozdemir T. Doppler ultrasonography versus venography in the detection of deep vein thrombosis in patients with pulmonary embolism. Journal of Thrombosis & Thrombolysis. 2006; 21(2):159-162. *(Guideline Ref ID OZBUDAK2006)*

182 Palareti G, Legnani C, Cosmi B, Valdre L, Lunghi B, Bernardi F et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation. 2003; 108(3):313-318. *(Guideline Ref ID PALARETI2003)*

183 Paterson D, I, Schwartzman K. Strategies incorporating spiral CT for the diagnosis of acute pulmonary embolism: a cost-effectiveness analysis. Chest. 2001; 119(6):1791-1800. *(Guideline Ref ID PATERSON2001)*

184 Pengo V, Legnani C, Noventa F, Palareti G, ISCOAT Study Group. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding. A Multicenter Inception Cohort Study. Thrombosis & Haemostasis. 2001; 85(3):418-422. *(Guideline Ref ID PENGO2001)*

185 Perez-de-Llano LA, Leiro-Fernandez V, Golpe R, Nunez-Delgado JM, Palacios-Bartolome A, Mendez-Marote L et al. Comparison of tinzaparin and acenocoumarol for the secondary prevention of venous thromboembolism: a multicentre, randomized study. Blood Coagulation & Fibrinolysis. 2010; 21(8):744-749. *(Guideline Ref ID PEREZDELLANO2010)*

186 Perlroth DJ, Sanders GD, Gould MK. Effectiveness and cost-effectiveness of thrombolysis in submassive pulmonary embolism. Archives of Internal Medicine. 2007; 167(1):74-80. *(Guideline Ref ID PERLROTH2007)*

187 Pernod G, Labarere J, Yver J, Satger B, Allenet B, Berremili T et al. EDUC'AVK: reduction of oral anticoagulant-related adverse events after patient education: a prospective multicenter open randomized study. Journal of General Internal Medicine. 2008; 23(9):1441-1446. *(Guideline Ref ID PERNOD2008)*

188 Perone N, Bounameaux H, Perrier A. Comparison of four strategies for diagnosing deep vein thrombosis: a cost-effectiveness analysis. American Journal of Medicine. 2001; 110(1):33-40. *(Guideline Ref ID PERONE2001)*

189 Perrier A, Buswell L, Bounameaux H, Didier D, Morabia A, de Moerloose P et al. Cost-effectiveness of noninvasive diagnostic aids in suspected pulmonary embolism. Archives of Internal Medicine. 1997; 157(20):2309-2316. *(Guideline Ref ID PERRIER1997)*

190 Perrier A, Nendaz MR, Sarasin FP, Howarth N, Bounameaux H. Cost-effectiveness analysis of diagnostic strategies for suspected pulmonary embolism including helical computed tomography. American Journal of Respiratory & Critical Care Medicine. 2003; 167(1):39-44. *(Guideline Ref ID PERRIER2003)*

191 Perrier A, Roy PM, Sanchez O, Le Gal G, Meyer G, Gourdier AL et al. Multidetector-row computed tomography in suspected pulmonary embolism. New England Journal of Medicine. 2005; 352(17):1760-1768. *(Guideline Ref ID PERRIER2005)*

192 Piccioli A, Lensing AW, Prins MH, Falanga A, Scannapieco GL, Ieran M et al. Extensive screening for occult malignant disease in idiopathic venous thromboembolism: a prospective randomized clinical trial. Journal of Thrombosis & Haemostasis. 2004; 2(6):884-889. *(Guideline Ref ID PICCIOLI2004)*

193 Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. Circulation. Department of Internal Medicine, Centre Hospitalier Universitaire de Lyon, France. laurent.pinede@chu-lyon.fr 2001; 103(20):2453-2460. *(Guideline Ref ID PINEDE2001A)*

194 Pini M, Aiello S, Manotti C, Pattacini C, Quintavalla R, Poli T et al. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. Thrombosis & Haemostasis. 1994; 72(2):191-197. *(Guideline Ref ID PINI1994)*

195 Prandoni P, Carnovali M, Marchiori A, Galilei Investigators. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. Archives of Internal Medicine. 2004; 164(10):1077-1083. *(Guideline Ref ID PRANDONI2004)*

196 Prandoni P, Lensing AW, Buller HR, Carta M, Cogo A, Vigo M et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lancet. 1992; 339(8791):441-445. *(Guideline Ref ID PRANDONI1992)*

197 Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M et al. The long-term clinical course of acute deep venous thrombosis. Annals of Internal Medicine. 1996; 125(1):1-7. *(Guideline Ref ID PRANDONI1996)*

198 Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Annals of Internal Medicine. 2004; 141(4):249-256. *(Guideline Ref ID PRANDONI2004A)*

199 Qanadli SD, Hajjam ME, Mesurolle B, Barre O, Bruckert F, Joseph T et al. Pulmonary embolism detection: prospective evaluation of dual-section helical CT versus selective pulmonary arteriography in 157 patients. Radiology. 2000; 217(2):447-455. *(Guideline Ref ID QANADLI2000)*

200 Ramacciotti E, Araujo GR, Lastoria S, Maffei FH, Karaoglan de Moura L, Michaelis W et al. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. Thrombosis Research. 2004; 114(3):149-153. *(Guideline Ref ID RAMACCIOTTI2004)*

201 Remy-Jardin M, Remy J, Deschildre F, Artaud D, Beregi JP, Hossein-Foucher C et al. Diagnosis of pulmonary embolism with spiral CT: comparison with pulmonary angiography and scintigraphy. Radiology. 1996; 200(3):699-706. *(Guideline Ref ID REMYJARDIN1996)*

202 Ricci P, Intrieri F, Cantisani V, Drudi FM, Fasoli F, Arduini F et al. Contrast-enhanced US in the assessment of the ilio-caval axis in deep venous thrombosis. Radiologia Medica. 2004; 107(5-6):506-514. *(Guideline Ref ID RICCI2004)*

203 Righini M, Le Gal G, Aujesky D, Roy PM, Sanchez O, Verschuren F et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. Lancet. 2008; 371(9621):1343-1352. *(Guideline Ref ID RIGHINI2008)*

204 Righini M, Nendaz M, Le Gal G, Bounameaux H, Perrier A. Influence of age on the cost-effectiveness of diagnostic strategies for suspected pulmonary embolism. Journal of Thrombosis & Haemostasis. 2007; 5(9):1869-1877. *(Guideline Ref ID RIGHINI2007)*

205 Rodger MA, Bredeson CN, Jones G, Rasuli P, Raymond F, Clement AM et al. The bedside investigation of pulmonary embolism diagnosis study: A double-blind randomized controlled trial comparing combinations of 3 bedside tests vs ventilation-perfusion scan for the initial investigation of suspected pulmonary embolism. Archives of Internal Medicine. 2006; 166(2):181-187. *(Guideline Ref ID RODGER2006B)*

206 Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, LE GG et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ Canadian Medical Association Journal. 2008; 179(5):417-426. *(Guideline Ref ID RODGER2008)*

207 Romera A, Cairols MA, Vila-Coll R, Marti X, Colome E, Bonell A et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. European Journal of Vascular & Endovascular Surgery. 2009; 37(3):349-356. *(Guideline Ref ID ROMERA2009)*

208 Royal College of Radiologists. Making the best use of clinical radiology services: referral guidelines. 6th edition. London: The Royal College of Radiologists; 2007 *(Guideline Ref ID RCR2007)*

209 Ruiz Y, Caballero P, Caniego JL, Friera A, Olivera MJ, Tagarro D et al. Prospective comparison of helical CT with angiography in pulmonary embolism: global and selective vascular territory analysis. Interobserver agreement. European Radiology. 2003; 13(4):823-829. *(Guideline Ref ID RUIZ2003)*

210 Ryan F, Byrne S, O'Shea S. Randomized controlled trial of supervised patient self-testing of warfarin therapy using an internet-based expert system. Journal of Thrombosis & Haemostasis. 2009; 7(8):1284-1290. *(Guideline Ref ID RYAN2009)*

211 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):476-486. *(Guideline Ref ID SARASIN1993)*

212 Sawicki PT. A structured teaching and self-management program for patients receiving oral anticoagulation. A randomized controlled trial. Journal of the American Medical Association. 1999; 281(2):145-150. *(Guideline Ref ID SAWICKI1999)*

213 Sawicki PT, Glaser B, Kleespies C, Stubbe J, Schmitz N, Kaiser T et al. Long-term results of patients' self-management of oral anticoagulation. Journal of Clinical and Basic Cardiology. 2003; 6(1-4):59-62. *(Guideline Ref ID SAWICKI2003)*

214 Schreiber D, Lin B, Liu G, Briese B, Hiestand B, Slattery D et al. Variation in therapy and outcomes in massive pulmonary embolism from the Emergency Medicine Pulmonary Embolism in the Real World Registry (EMPEROR). Academic Emergency Medicine. 2009; 16(Suppl 1):S77-S78. *(Guideline Ref ID SCHREIBER2009)*

215 Schulman S, Granqvist S, Holmstrom M, Carlsson A, Lindmarker P, Nicol P et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. New England Journal of Medicine. Department of Internal Medicine at Karolinska Hospital, Stockholm, Sweden. 1997; 336(6):393-398. *(Guideline Ref ID SCHULMAN1997A)*

216 Schulman S, Granqvist S, Juhlin-Dannfelt A, Lockner D. Long-term sequelae of calf vein thrombosis treated with heparin or low-dose streptokinase. Acta Medica Scandinavica. 1986; 219(4):349-357. *(Guideline Ref ID SCHULMAN1986)*

217 Schulman S, Lockner D, Juhlin-Dannfelt A. The duration of oral anticoagulation after deep vein thrombosis. A randomized study. Acta Medica Scandinavica. 1985; 217(5):547-552. *(Guideline Ref ID SCHULMAN1985A)*

218 Schunemann HJ, Guyatt GH. Commentary--goodbye M(C)ID! Hello MID, where do you come from? Health Services Research. 2005; 40(2):593-597. *(Guideline Ref ID SCHUNEMANN2005)*

219 Schunemann HJ, Puhan M, Goldstein R, Jaeschke R, Guyatt GH. Measurement properties and interpretability of the Chronic respiratory disease questionnaire (CRQ). Copd: Journal of Chronic Obstructive Pulmonary Disease. 2005; 2(1):81-89. *(Guideline Ref ID SCHUNEMANN2005A)*

220 Schweizer J, Elix H, Altmann E, Hellner G, Forkmann L. Comparative results of thrombolysis treatment with rt-PA and urokinase: a pilot study. Vasa - Journal of Vascular Diseases. 1998; 27(3):167-171. *(Guideline Ref ID SCHWEIZER1998)*

221 Schweizer J, Kirch W, Koch R, Elix H, Hellner G, Forkmann L et al. Short- and long-term results after thrombolytic treatment of deep venous thrombosis. Journal of the American College of Cardiology. 2000; 36(4):1336-1343. *(Guideline Ref ID SCHWEIZER2000)*

222 Sharifi M, Mehdipour M, Bay C, Smith G, Sharifi J. Endovenous therapy for deep venous thrombosis: the TORPEDO trial. Catheterization & Cardiovascular Interventions. 2010; 76(3):316-325. *(Guideline Ref ID SHARIFI2010)*

223 Shiver SA, Lyon M, Blaivas M, Adhikari S. Prospective comparison of emergency physician-performed venous ultrasound and CT venography for deep venous thrombosis. American Journal of Emergency Medicine. 2010; 28(3):354-358. *(Guideline Ref ID SHIVER2010)*

224 Shorr AF, Jackson WL, Moores LK, Warkentin TE. Minimizing costs for treating deep vein thrombosis: the role for fondaparinux. Journal of Thrombosis & Thrombolysis. 2007; 23(3):229-236. *(Guideline Ref ID SHORR2007)*

225 Sidhu P, O'Kane HO. Self-managed anticoagulation: results from a two-year prospective randomized trial with heart valve patients. Annals of Thoracic Surgery. 2001; 72(5):1523-1527. *(Guideline Ref ID SIDHU2001)*

226 Siebenhofer A, Rakovac I, Kleespies C, Piso B, Didjurgeit U. Self-management of oral anticoagulation in the elderly: rationale, design, baselines and oral anticoagulation control after one year of follow-up. A randomized controlled trial. Thrombosis & Haemostasis. 2007; 97(3):408-416. *(Guideline Ref ID SIEBENHOFER2007)*

227 Simonneau G, Charbonnier B, Decousus H, Planchon B, Ninet J, Sie P et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. Archives of Internal Medicine. 1993; 153(13):1541-1546. *(Guideline Ref ID SIMONNEAU1993)*

228 Simonneau G, Sors H, Charbonnier B, Page Y, Laaban JP, Azarian R et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. New England Journal of Medicine. 1997; 337(10):663-669. *(Guideline Ref ID SIMONNEAU1997)*

229 Simpson EL, Stevenson MD, Rawdin A, Papaioannou D. Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis. Health Technology Assessment. 2009; 13(2):iii-iix. *(Guideline Ref ID SIMPSON2009)*

230 Smith KJ, Monsef BS, Ragni MV. Should female relatives of factor V Leiden carriers be screened prior to oral contraceptive use? A cost-effectiveness analysis. Thrombosis & Haemostasis. 2008; 100(3):447-452. *(Guideline Ref ID SMITH2008)*

231 Sood S, Negi A, Dhiman DS, Sood RG, Negi PC, Sharma S. Role of CT angiography in pulmonary embolism and its comparative evaluation with conventional pulmonary angiography. Indian Journal of Radiology and Imaging. 2006; 16(2):215-219. *(Guideline Ref ID SOOD2006)*

232 Stain M, Schonauer V, Minar E, Bialonczyk C, Hirschl M, Weltermann A et al. The post-thrombotic syndrome: risk factors and impact on the course of thrombotic disease. Journal of Thrombosis & Haemostasis. 2005; 3(12):2671-2676. *(Guideline Ref ID STAIN2005)*

233 Steeghs N, Goekoop RJ, Niessen RW, Jonkers GJ, Dik H, Huisman MV. C-reactive protein and D-dimer with clinical probability score in the exclusion of pulmonary embolism. British Journal of Haematology. 2005; 130(4):614-619. *(Guideline Ref ID STEEGHS2005)*

234 Stein PDA. Tissue plasminogen activator for the treatment of acute pulmonary embolism. Chest. 1990; 97(3):528-533. *(Guideline Ref ID STEIN1990)*

235 Stevens SM, Gregory EC, Woller SC, Li L, Bennett ST, Egger M et al. The use of a fixed high sensitivity to evaluate five D-dimer assays' ability to rule out deep venous thrombosis: a novel approach. British Journal of Haematology. 2005; 131(3):341-347. *(Guideline Ref ID STEVENS2005)*

236 Subramaniam RM, Chou T, Heath R, Allen R. Importance of pretest probability score and D-dimer assay before sonography for lower limb deep venous thrombosis. American Journal of Roentgenology. 2006; 186(1):206-212. *(Guideline Ref ID SUBRAMANIAM2006C)*

237 Subramaniam RM, Heath R, Cox K, Chou T, Stewart J, Sleigh J. Does an immunochromatographic D-dimer exclude acute lower limb deep venous thrombosis? Emergency Medicine Australasia. 2006; 18(5-6):457-463. *(Guideline Ref ID SUBRAMANIAM2006A)*

238 Subramaniam RM, Snyder B, Heath R, Tawse F, Sleigh J. Diagnosis of lower limb deep venous thrombosis in emergency department patients: performance of Hamilton and modified Wells scores. Annals of Emergency Medicine. 2006; 48(6):678-685. *(Guideline Ref ID SUBRAMANIAM2006)*

239 Sunderji R, Campbell L, Shalansky K, Fung A, Carter C, Gin K. Outpatient self-management of warfarin therapy: a pilot study. Pharmacotherapy. 1999; 19(6):787-793. *(Guideline Ref ID SUNDERJI1999)*

240 Sunderji R, Gin K, Shalansky K, Carter C, Chambers K, Davies C et al. A randomized trial of patient self-managed versus physician-managed oral anticoagulation. Canadian Journal of Cardiology. 2004; 20(11):1117-1123. *(Guideline Ref ID SUNDERJI2004)*

241 Taborski U, Wittstamm FJ, Bernardo A. Cost-effectiveness of self-managed anticoagulant therapy in Germany. Seminars in Thrombosis & Hemostasis. 1999; 25(1):103-107. *(Guideline Ref ID TABORSKI1999)*

242 Ten Cate-Hoek AJ, Toll DB, Buller HR, Hoes AW, Moons KG, Oudega R et al. Cost-effectiveness of ruling out deep venous thrombosis in primary care versus care as usual. Journal of Thrombosis & Haemostasis. 2009; 7(12):2042-2049. *(Guideline Ref ID TENCATEHOEK2009)*

243 Tomkowski WZ, Davidson BL, Wisniewska J, Malek G, Kober J, Kuca P et al. Accuracy of compression ultrasound in screening for deep venous thrombosis in acutely ill medical patients. Thrombosis & Haemostasis. 2007; 97(2):191-194. *(Guideline Ref ID TOMKOWSKI2007)*

244 Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P et al. Guidelines for the diagnosis and management of acute pulmonary embolism. Revista Espanola De Cardiologia English Edition. 2008; 61(12):1330. *(Guideline Ref ID TORBICKI2008B)*

245 Tsapogas MJ, Peabody RA, Wu KT, Karmody AM, Devaraj KT, Eckert C. Controlled study of thrombolytic therapy in deep vein thrombosis. Surgery. 1973; 74(6):973-984. *(Guideline Ref ID TSAPOGAS1973)*

246 Turpie AG, Levine MN, Hirsh J, Ginsberg JS, Cruickshank M, Jay R et al. Tissue plasminogen activator (rt-PA) vs heparin in deep vein thrombosis. Results of a randomized trial. Chest. 1990; 97(4 Suppl):172S-175S. *(Guideline Ref ID TURPIE1990)*

247 Valette F, Hoffmeyer U, Lloyd A. Economic evaluation of the use of tinzaparin in the treatment of deep vein thrombosis. British Journal of Medical Economics. 1995; 8:111-123. *(Guideline Ref ID VALETTE1995)*

248 van Beek EJR, Schenk BE, Michel BC, van den Ende B, Brandies D, van der Heide YT et al. The role of plasma D-dimer concentration in the exclusion of pulmonary embolism. British Journal of Haematology. 1996; 92(3):725-732. *(Guideline Ref ID VANBEEK1996)*

249 van Belle A, Buller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. Journal of the American Medical Association. 2006; 295(2):172-179. *(Guideline Ref ID VANBELLE2006)*

250 van Erkel AR, Pattynama PMT. Cost-effective diagnostic algorithms in pulmonary embolism: an updated analysis. Academic Radiology. 1998; 5 Suppl 2:S321-S327. *(Guideline Ref ID VANERKEL1998)*

251 van Erkel AR, van Rossum AB, Bloem JL, Kievit J, Pattynama PMT. Spiral CT angiography for suspected pulmonary embolism: a cost effectiveness analysis. Radiology. 1996; 201(1):29-36. *(Guideline Ref ID VANERKEL1996)*

252 van Sluis GL, Sohne M, El Kheir DY, Tanck MW, Gerdes VE, Buller HR. Family history and inherited thrombophilia. Journal of Thrombosis and Haemostasis. 2006; 4(10):2182-2187. *(Guideline Ref ID VANSLUIS2006)*

253 Veiga F, Escriba A, Maluenda MP, Lopez RM, Margalet I, Lezana A et al. Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. Thrombosis & Haemostasis. 2000; 84(4):559-564. *(Guideline Ref ID VEIGA2000)*

254 Verhaeghe R, Besse P, Bounameaux H, Marbet GA. Multicenter pilot study of the efficacy and safety of systemic rt-PA administration in the treatment of deep vein thrombosis of the lower extremities and/or pelvis. Thrombosis Research. 1989; 55(1):5-11. *(Guideline Ref ID VERHAEGHE1989A)*

255 Verhovsek M, Douketis JD, Yi Q, Shrivastava S, Tait RC, Baglin T et al. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. Annals of Internal Medicine. 2008; 149(7):481-490. *(Guideline Ref ID VERHOVSEK2008)*

256 Voller H, Glatz J, Taborski U, Bernardo A, Dovifat C, Heidinger K. Self-management of oral anticoagulation in nonvalvular atrial fibrillation (SMAAF study). Zeitschrift Für Kardiologie. 2005; 94(3):182-186. *(Guideline Ref ID VOLLER2005)*

257 Vreim CE, Saltzmann HA, Alavai A, Greenspan RH, Hales CA, Stein PD et al. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). Journal of the American Medical Association. 1990; 263(20):2753-2759. *(Guideline Ref ID VREIM1990)*

258 Wang F, Fang W, Ly B, Lu JG, Xiong CM, Ni XH et al. Comparison of lung scintigraphy with multi-slice spiral computed tomography in the diagnosis of pulmonary embolism. Clinical Nuclear Medicine. 2009; 34(7):424-427. *(Guideline Ref ID WANG2009)*

259 Watson LI, Armon MP. Thrombolysis for acute deep vein thrombosis. Cochrane Database of Systematic Reviews. 2004;(Issue 4):CD002783. *(Guideline Ref ID WATSON2004)*

260 Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. 1997; 350(9094):1795-1798. *(Guideline Ref ID WELLS1997)*

261 Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. New England Journal of Medicine. 2003; 349(13):1227-1235. *(Guideline Ref ID WELLS2003A)*

262 Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thrombosis & Haemostasis. 2000; 83(3):416-420. *(Guideline Ref ID WELLS2000)*

263 Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Annals of Internal Medicine. 2001; 135(2):98-107. *(Guideline Ref ID WELLS2001)*

264 Wells PS, Ginsberg JS, Anderson DR, Kearon C, Gent M, Turpie AG et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Annals of Internal Medicine. 1998; 129(12):997-1005. *(Guideline Ref ID WELLS1998)*

265 White RH, McCurdy SA, von Marensdorff H, Woodruff DE, Jr., Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy. A randomized, prospective study. Annals of Internal Medicine. 1989; 111(9):730-737. *(Guideline Ref ID WHITE1989)*

266 Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. Archives of Internal Medicine. 2001; 161(1):92-97. *(Guideline Ref ID WICKI2001)*

267 Winer-Muram HT, Rydberg J, Johnson MS, Tarver RD, Williams MD, Shah H et al. Suspected acute pulmonary embolism: evaluation with multi-detector row CT versus digital subtraction pulmonary arteriography. Radiology. 2004; 233(3):806-815. *(Guideline Ref ID WINERMURAM2004)*

268 Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest. 2002; 121(3):877-905. *(Guideline Ref ID WOOD2002)*

269 Wu O, Robertson L, Twaddle S, Lowe G, Clark P, Walker I et al. Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis. British Journal of Haematology. 2005; 131(1):80-90. *(Guideline Ref ID WU2005)*

270 Yamaki T, Nozaki M, Sakurai H, Takeuchi M, Soejima K, Kono T. Prospective evaluation of a screening protocol to exclude deep vein thrombosis on the basis of a combination of quantitative D-dimer testing and pretest clinical probability score. Journal of the American College of Surgeons. 2005; 201(5):701-709. *(Guideline Ref ID YAMAKI2005)*

16 Glossary

Term	Definition
Absolute effect	The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study.
Absolute risk reduction (Risk difference)	See absolute effect.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acquired thrombophilia	A thrombophilia that is not inherited. For example, antiphospholipid syndrome. See 'heritable thrombophilia' and 'antiphospholipid syndrome'.
Activated partial thromboplastin time (APTT)	The time needed for plasma to form a fibrin clot after the addition of calcium and a phospholipid reagent; used to evaluate the intrinsic clotting system. The dose of UFH is titrated to the results of this. See also 'monitoring' and 'international normalised ratio (INR)'.
Active cancer	Those with metastatic disease and those receiving chemotherapy.[153]
Adherence	The extent to which the patient's behaviour matches agreed recommendations from the prescriber'. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the prescriber's recommendation (from CG76). See also 'compliance' and 'concordance'.
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.
Anticoagulant	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.
Anti-embolism stockings	Anti-embolism stockings are a type of compression stocking designed specifically to prevent VTE. The compression delivered to the ankle is in the range of 18-24mmHg corresponding to British standard hosiery Class 2 and European standard hosiery Class 1. Other types of compression stocking are used to treat, rather than prevent, conditions that affect blood flow in the legs, including DVT. See also "graduated compression stockings".
Antiphospholipid syndrome	An acquired disorder of coagulation that causes blood clots (thrombosis) in both arteries and veins as well as pregnancy-related complications. The syndrome occurs due to the autoimmune production of antibodies against phospholipid-binding proteins. See also "heritable thrombophilia" and "thrombophilia".
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	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice

Term	Definition
(AGREE)	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.
Atrial Fibrillation (AF)	The most common cardiac arrhythmia, usually involving an irregular, rapid heart rate.
Audit	See 'Clinical audit'.
Available case analysis (ACA)	An analysis in which data are analysed for every participant for whom the outcome was obtained.
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.
Calf vein DVT, Distal DVT	A DVT which involves the veins of the calf but not higher veins. See 'proximal DVT'.
Cancer associated VTE	A VTE event occurring in someone with active cancer.
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.
Catheter/vein directed thrombolysis	Direct intrathrombus injection of the thrombolytic agent.
Charlotte's Rule	This is a clinical prediction rule for PE. See Clinical scores.
Chronic thromboembolic pulmonary hypertension	Persistent pulmonary hypertension caused by obstruction or narrowing of pulmonary arteries by an unresolved embolus or multiple small pulmonary emboli.
Class (of drugs)	A group of drugs with the same or similar mechanism of action; these drugs may or may not have the same basic chemical structure. However, there may be differences between drugs within a class (for example, in side-effect profile).
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

Term	Definition
	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 importance	This refers to whether the size of the effect observed between groups. If the MID is less than the lower limit of the 95% CI, results are likely to be statistically significant and clinically important. If the MID is greater than the upper limit of the 95% CI, results are likely to be clinically unimportant. If the MID lies within the limits of the 95% CI, it is unclear if the effect is clinically important or not[33]
Clinical probability scores	This includes the Wells score (original and revised), Charlotte's rule and the Geneva score (original and revised). These have also been called 'clinical scores' and 'clinical prediction rules' in the literature.
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.
Computed tomography (CT) scan	A scan that can be used in the diagnosis of PE. A scan which produces images of a cross sectional plane of the body. The scan is produced by computer synthesis of x-ray images taken in many different directions in a given plane.
Computed tomography pulmonary angiography (CTPA)	A test that can be used in the diagnosis of PE. It uses computed tomography to visualise the pulmonary arteries.
Comorbidity	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 the patient's behaviour matches the prescribers' recommendations (from CG76). See also 'adherence' and 'concordance'.
Compression hosiery/stockings	See 'anti-embolism stockings' and 'graduated compression stockings'
Concordance	Initially applied to the consultation process in which prescriber and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine-taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence (from CG76). See also 'adherence' and 'compliance'.
Conference proceedings	Compilation of papers presented at a conference.

Term	Definition
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.
Continuation phase of (anticoagulation) treatment	The phase of anticoagulation treatment after the initial phase. This is usually with VKA treatment, though LMWH may be used particularly in cancer patients. See also 'initial phase of treatment' and 'long-term treatment'.
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. For non- pharmacological interventions, some studies may use the routine care or usual care as the control group to test the effect of changing one or more elements of the care.
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).
Credible interval	The Bayesian equivalent of a confidence interval.

Term	Definition
D- dimer	A product that is formed in the body when a blood clot (such as those found in PE or DVT) is broken down. A laboratory or point of care test can be done to assess the concentration of D- dimer in a person's blood. The results from this test can be used as part of pre- test probability assessment when there is suspicion of DVT or PE.
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 further away from the centre of the body than another part.
Dominance (in cost-effectiveness analysis)	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/masked 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.
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'.
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 profile	A table summarising, for each important clinical outcome, the quality of the evidence and the outcome data (part of the GRADE approach). See

Term	Definition
	'GRADE'.
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.
Evidence statement	A brief summary of one finding from a review of evidence that a clinical guideline is based on.
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 adviser	A person who has specialist knowledge in a particular area related to a clinical guideline. The expert adviser attends Guideline Development Group meetings to give advice, but is not a full member of the group.
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.
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.
Generic name	The general non-proprietary name of a drug or device.
Geneva score	This is a clinical prediction rule for PE. See Clinical scores.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations.
Grading (of evidence)	A code given to a study or other evidence, indicating the quality and generalisability of the research. The highest grade evidence will usually be obtained from randomised controlled trials.
Gold standard	See 'Reference standard'.
Goodness-of-fit	How well a statistical model or distribution compares with the observed data.
Graduated compression stockings (GCS) or hosiery	Compression stockings, also called compression hosiery, are supportive stockings designed to facilitate compression therapy, a technique that helps improve circulation to relieve a range of medical conditions such as varicose veins or DVT depending on the pressure applied at the ankle. Patients are measured prior to the use of stockings to ensure they are fitted correctly. For the purpose of preventing post –thrombotic syndrome in patients with DVT the stockings should have a compression at the ankle of between 25-35 mmHg corresponding to British standard hosiery Class 3 and European standard hosiery Class 2.

Term	Definition
	See ‘antiembolism stockings’.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems.
Guideline development group (GDG)	A group of healthcare professionals, patients and carers, and technical staff who develop the recommendations for a clinical guideline. The National Collaborating Centre (NCC) responsible for developing the guideline recruits a GDG to work on the guideline. NCC staff review the evidence and support the GDG. The group writes draft guidance, and then revises it after a consultation with stakeholders.
Guideline review panel	A panel of independent experts who comment on the draft scope for a clinical guideline and check the full guideline. The panel pays particular attention to how the Guideline Development Group has responded to comments received during consultation. The members include healthcare professionals, and representatives of the healthcare industry and patients.
Haemodynamically stable PE	This is when a patient with PE also has a normal blood pressure. The haemodynamically stable patient subgroup will include groups previously referred to as normotensive, non-massive, or sub-massive PE . Within this group there are two subgroups of patients that may be considered separately by clinicians, according to whether there is evidence of right heart strain or injury. See also ‘pulmonary embolus’.
Haemodynamically unstable PE	This is when a patient with PE also has a low blood pressure defined by a systolic blood pressure < 90mmHg or a pressure drop of ≥40 mmHg for >15 minutes if not caused by an arrhythmia, hypovolaemia or sepsis [244,268]. The haemodynamically unstable patient subgroup will include groups previously referred to as massive PE. See also ‘pulmonary embolus’.
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 (HRQL)	A combination of an individual’s physical, mental and social well-being; not merely the absence of disease.
Heparin-induced thrombocytopenia (HIT)	A 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.
Heritable thrombophilia	An inherited tendency to develop thrombosis. The most common ones are factor V Leiden and a mutation in prothrombin. The rare forms are antithrombin III deficiency, protein C deficiency and protein S deficiency.
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.
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.
Idiopathic	Of unknown cause, see unprovoked.
Implementation	The process of putting guidance into practice.

Term	Definition
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide CIs around the estimate of effect.
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).
Indirectness	This is one of the elements reviewed in the GRADE system. In directness is considered present when the available evidence is different to the review question being addressed or population where the recommendation would be made, in terms of population, intervention, comparison and outcomes. See GRADE.
Initial phase of (anticoagulation) treatment	This covers the period from the confirmation of VTE diagnosis until the continuation phase of treatment is established. See also ‘continuation phase of treatment’.
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.
International Normalised Ratio (INR)	A way of measuring how fast the blood clots when the patient is taking a VKA. The prothrombin time of the patient is compared to the prothrombin time of a control blood sample and expressed as a ratio, which is then transformed into an international normalised ratio to take account of the reagent used. This measurement is used to monitor the adequacy of anticoagulation for patients who are on VKA treatment. See ‘monitoring’, ‘self-monitoring’ and ‘self-management’.
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.

Term	Definition
Key priorities for implementation	Up to 10 recommendations from a clinical guideline that should be implemented first because they will have the biggest impact. They are chosen by the Guideline Development Group.
Length of stay (LOS)	The total number of days a participant stays in hospital.
Licence	See 'Marketing authorisation'.
Life year (LY)	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.
Long-term (anticoagulation) treatment	Prolonged treatment (for an indefinite period) beyond the continuation phase in selected patients. See also 'continuation phase of treatment'.
Major bleeding	Bleeding that is overt and has one or more of the following characteristics: a decrease in haemoglobin concentration by at least 2.0g/dL; the need for transfusion of at least 1-2 units of blood; intracranial or retroperitoneal bleeding; caused an interruption of therapy; or led to death.
Marketing authorisation	An authorisation that covers all the main activities associated with the marketing of a medicinal product. Medicines that meet the standards of safety, quality and efficacy set by the Medicines and Healthcare products Regulatory Agency are granted a marketing authorisation (previously a product licence), which is normally necessary before they can be prescribed or sold.
Mechanical	Physical (as opposed to chemical) agent. See 'Graduated compression stockings' (GCS) ,'vena caval filters' and 'mechanical thrombectomy'.
Mechanical thrombectomy/Pharmaco-mechanical thrombolysis	A technique that breaks up the thrombus by using mechanical devices inserted via a catheter, often combined with thrombolysis using drug agents. See thrombolysis and thrombolytics.
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.
Minimal important difference (MID)	The MID is the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in the management (insert refs). This term was adapted from the earlier definition used for MCID (minimal clinically important difference) with the term "clinical" removed to emphasise on the importance of patient perspective. The term "MID" has been adopted by GRADE. In this guidance, we also use the term to refer to the clinically important thresholds or harms when considering imprecision.
Monitoring	In the context of this guideline monitoring refers to the regular review of a patient's clinical status with respect to the anticoagulation treatment that the patient receives. This includes reviewing the patient's INR if they are receiving VKAs, or reviewing the patient's apparent prothrombin time (aPTT) if they are receiving UFH. A review of the patient's coagulation status can be carried out by the patient, a carer or by a member of the healthcare team.

Term	Definition
	See also ‘self monitoring’ and ‘self management’.
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.
Near patient testing	See ‘point of care testing’
Negative predictive value	The proportion of people with a negative test result who are correctly diagnosed.
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 (OR)	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.
Operating costs	Ongoing costs of carrying out an intervention, excluding capital costs.
Open surgical thrombectomy	Removal of blood clot by an open surgical technique.
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’.
Peer review	A process where research is scrutinised by experts that have not been involved in the design or execution of the studies.
Per- protocol analysis	An analysis in which the data of individuals who completed the trial and adhered to (or received some of) their allocated intervention are analysed.
Pharmacological thrombolytics/thrombolysis	Agents/drugs such as streptokinase, urokinase and recombinant tissue-type plasminogen activator (r-t-PA) used in the treatment of VTE to actively break up clot leading to rapid normalisation of vascular blood flow.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing questions about interventions that divides each question into four components: the patients (the population under study); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
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.

Term	Definition
Planar lung scintigraphy	See 'ventilation perfusion scans'.
Point-of-care testing (POCT)	Medical testing, using analytical devices (including test kits and analysers), that is provided near to the patient. The point of care test may be carried out by a member of the healthcare team, or a non-medical individual in a setting distinct from a normal hospital laboratory. This allows for more convenient testing and faster availability of results. In this guideline, this term is used to describe devices for D-dimer or INR testing.
Positive predictive value	The proportion of people with a positive test result who actually have the disease or characteristic. This is also known as "post-test probability".
Post-thrombotic (Post-phlebitic) Syndrome (PTS)	PTS refers to the chronic pain, swelling, and occasional ulceration of the skin of the leg that occurs as a consequence of previous venous thrombosis. The Villalta score allocates points for signs (pretibial oedema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia, redness) and symptoms (pain, cramps, heaviness, paraesthesia, pruritus) of the PTS. Each sign or symptom receives points (0-none, 1-mild, 2-moderate, 3-severe). Severe PTS is classified when the Villalta score is 5 or above or when there is an ulcer.
Pre-test probability (testing)	The pre-test probability is the prevalence of a condition in a specific population. Clinical prediction rules such as the Wells score have criteria which help to classify patients presenting with symptoms of DVT or PE into groups with different risks (probability)of getting DVT or PE. These are used before further tests and are also known as "pre-test probability tests". See also 'Wells score'.
Prevalence	The total number of cases of the risk factor in the population at a given time, (or the total number of cases in the population divided by the number of individuals in the population). It is used as an estimate of how common a disease is within a population over a certain period of time.
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. This is now mostly known as 'marketing authorisation'.
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.
Prothrombin time (PT)	The time taken for blood to clot in a sample of blood, to which calcium and thromboplastin have been added. It tests the extrinsic pathway of blood coagulation. See 'International normalised ratio (INR)'.
Provoked VTE	VTE which occurred in the presence of an antecedent (within 3 months) and transient major clinical risk factor for VTE (for example surgery, trauma, significant immobility and pregnancy or puerperium). The GDG also considered VTE that occurred in association with hormonal therapy (oral contraceptive or hormone replacement therapy) to be provoked as it

Term	Definition
	has been shown that these patients are at a lower risk of recurrence[16].See also 'unprovoked VTE'
Proximal	Refers to a part of the body that is closer to the centre of the body than another part.
Proximal DVT	DVT in the popliteal vein or above. Proximal DVT is sometimes referred to as 'above-knee DVT'.
Proximal leg vein ultrasound scan	Ultrasound scans in the leg veins; from the popliteal vein and above, including the common femoral vein.
Pulmonary embolism (PE)	A blood clot that breaks off from the deep veins and travels round the circulation to block the pulmonary arteries Most deaths arising from DVT are caused by PE. See 'haemodynamically unstable PE' and 'haemodynamically stable PE'.
Pulmonary hypertension	See 'Chronic thromboembolic pulmonary hypertension'.
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-year (QALY)	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 (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.
Recommendations	Formal, numbered paragraphs in NICE clinical guidelines that give specific advice on the appropriate treatment and care of people with specific diseases and conditions within the NHS.
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.
Renal impairment	Reduced renal function, may be acute or chronic. An estimated glomerular filtration rate (eGFR) less than 90mL/minute/1.73m^2 indicates a degree of renal impairment in chronic kidney disease. For the purposes of this guideline the GDG defined "severe renal impairment" as an estimated glomerular filtration rate (eGFR) less than 30mL/minute/1.73m$^{2.}$

Term	Definition
Research recommendation	Recommendations for future research covering questions relating to an uncertainty or evidence gap that has been identified during the guideline development process.
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.
Review protocol	A document that outlines the background, objectives and planned methods for a systematic review.
Review question	A structured question about treatment and care that is formulated by the Guideline Development Group from a key clinical issue in the scope to guide the systematic review. A review question has four components: • patients (the population under study) • interventions (what is being done) • comparisons (other main treatment options) • outcomes.
Scope	Document created at the start of producing a piece of guidance outlining what the guidance will and will not cover. Organisations registered as stakeholders, can comment on the draft scope during a consultation period. The final version of the scope – taking into account comments from the consultation – is used as a starting point for developing the guidance.
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.
Self-management	In the context of this guideline, this refers to patients testing their own INR and adjusting their own dose of oral anticoagulant. See also 'self monitoring'.
Self monitoring	In the context of the guideline, this refers to patients testing their own INR and reporting the INR value to a clinician who then gives advice about change of dosage of oral anticoagulant. See 'monitoring' and 'self management'.
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. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter

Term	Definition
	on the results of the study. 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. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. 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).
Severe renal impairment	An estimated glomerular filtration rate (eGFR) less than 30mL/minute/1.73m$^{2.}$ See also "renal impairment".
Significantly reduced mobility	In terms of risk of VTE, this was defined in the VTE prophylaxis guideline as 'patients who are bed bound, unable to walk unaided or likely to spend a substantial proportion of their day in bed or in a chair'.
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.
Study quality	The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.
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.
Systemic thrombolysis	Thrombolytic agent (for example streptokinase)that reaches the target thrombus via the systemic circulation.
Thrombolysis Or thrombolytics	Treatments for VTE that actively break up clot resulting in rapid normalisation of vascular blood flow. Drugs that result in clot breakdown are termed thrombolytics. See also 'Catheter directed thrombolysis', 'systemic thrombolysis', 'Pharmacological thrombolytics', 'mechanical thrombolysis' and 'open surgical thrombectomy'.
Thrombophilia	The genetic or acquired prothrombotic states that increase the tendency to VTE. See also 'anti-phospholipid syndrome' and 'heritable thrombophilia'.
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.
Trellis device	This is used in catheter directed thrombolysis. It is a catheter with two balloons, one deployed above and one below the clot, to keep the thrombolytic agent only where it is needed.

Term	Definition
Unprovoked VTE	DVT or PE in a patient with no antecedent major clinical risk factor for VTE (see 'Provoked deep vein thrombosis or pulmonary embolism' above) who is not having hormonal therapy (oral contraceptive or hormone replacement therapy). Patients with active cancer, thrombophilia or a family history of VTE should also be considered as having an unprovoked episode because these underlying risks will remain unchanged in the patient.
Usual care	The term "usual care" is sometimes used to describe the care received by the control group in the clinical evidence reviewed. The control group(s) in the studies reviewed had a control groups receiving "routine", "usual" or "standard" care, and test the effectiveness of the new intervention by adding it to the usual care. This term is used within this guideline whenever there are differences between studies in the interventions and controls used, for example in the studies of patient education and self monitoring of warfarin. See also "control".
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.
Vena caval filter	A device inserted into a major vein to prevent a blood clot from entering the lungs. See also 'temporary vena caval filter'
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.
Ventilation perfusion scans- planar lung scintigraphy (V/Q)	A scan used in the diagnosis of PE. The scan involves the patient breathing in a gas/ aerosol containing isotopic material, and also receiving an injection of isotopic contrast material. A gamma camera is then used in order to visualise the location the isotopic material from the gas/ aerosol and injection is in the lungs.
Ventilation perfusion scans- single photon emission computed tomography (V/Q SPECT)	The patient inhales a gas/aerosol and receives an injection containing isotopes as in the ventilation perfusion scans- planar lung scintigraphy. A more modern gamma camera is used; the camera rotates around the patient and collects images in different planes. This allows 3 dimensional images and images in any plane to be viewed.
Vitamin K antagonist (VKA)	An oral treatment that inhibits vitamin K thus preventing coagulation. These include coumarins, such as warfarin, and phenindione.
Wells score	The Wells score (also known as 'Well's Criteria,) may refer to one of two clinical prediction rules in clinical medicine; one for diagnosing the probability of DVT and the other PE. There are a few versions of these scores available. This guideline has recommended the two level DVT Wells score[261] and the two level PE Wells score[262]. See also 'Clinical probability scores'.