Venous thromboembolism:

reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital

METHODS, EVIDENCE & GUIDANCE

Produced by the National Collaborating Centre for Acute Care

Contents

2 Summary of recommendations

Below are the recommendations that the Guideline Development Group (GDG) selected as the key priorities for implementation followed by the full list of recommendations.

2.1 Key priorities for implementation

The GDG identified ten key priorities for implementation. The decision was made after voting by the GDG. They selected recommendations that would:

- Have a high impact on outcomes that are important to patients **(A)**
- Have a high impact on reducing variation in care and outcomes **(B)**
- Lead to a more efficient use of NHS resources **(C)**
- Promote patient choice **(D)**
- Promote equalities. **(E)**

In doing this the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- Requires changes in service delivery (**W**)
- Requires retraining of professionals or the development of new skills and competencies (**X**)
- Affects and needs to be implemented across various agencies or settings (complex interactions) (**Y**)
- May be viewed as potentially contentious, or difficult to implement for other reasons (**Z**)

For each key recommendation listed below, the selection criteria and implementation support points are indicated by the use of the letters shown in brackets above.

- Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).

(Selection Criteria: A, B, C; Implementation support: W, X Y)

- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more **or**
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in **Box 1**.

(Selection Criteria: A, B, C; Implementation support: W, X Y)

- Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - have one or more risk factors shown in **Box 1**.

(Selection Criteria: A, B, C; Implementation support: W, X Y

- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in **Box 2,** unless the risk of VTE outweighs the risk of bleeding.

**Consult the summary of product characteristics for the pharmacological prophylaxis being used or planned for further details.*

(**Selection Criteria: A, B, C, E; Implementation support: X, Y)**

- Reassess patients' risk of bleeding and VTE within 24 hours of admission and whenever the clinical situation changes, to:
  - ensure that the methods of VTE prophylaxis used are suitable
  - ensure that VTE prophylaxis is being used correctly
  - identify adverse events resulting from VTE prophylaxis.

(Selection Criteria: A, B, C, E; Implentation support: W, X, Y)

- Encourage patients to mobilise as soon as possible.

(Selection Criteria: A, B, C; Implentation support: Y)

- Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE (see section 2.2.1). Choose any one of:
    - fondaparinux sodium
    - LMWH*
    - UFH (for patients with renal failure).

  Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

**At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH.* Informed consent for off-label use should be obtained and documented.

(Selection Criteria: A, B, C, E; Implentation support: X)

- Before starting VTE prophylaxis, offer patients and/or their families or carers verbal and written information on:
    - the risks and possible consequences of VTE
    - the importance of VTE prophylaxis and its possible side effects
    - the correct use of VTE prophylaxis (for example, anti-embolism stockings, foot impulse or intermittent pneumatic compression devices)
    - how patients can reduce their risk of VTE (such as keeping well hydrated and, if possible exercising and becoming more mobile)

(Selection Criteria: A, B, C, D, E; Implementation Support: W, X, Y, Z)

- As part of the discharge plan, offer patients and/or their families or carers verbal and written information on:
    - the signs and symptoms of deep vein thrombosis and pulmonary embolism
    - the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)
    - the importance of using VTE prophylaxis correctly and continuing treatment for the recommended duration (if discharged with prophylaxis)
    - the signs and symptoms of adverse events related to VTE prophylaxis (if discharged with prophylaxis)
    - the importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis)
    - the importance of seeking medical help if deep vein thrombosis, pulmonary embolism or another adverse events is suspected.

(Selection Criteria: A,B, C, D, E; Implementation Support: W, X, Y, Z)

2.2 The complete list of clinical practice recommendations

2.2.1 Assessing the risks of VTE and bleeding

- Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).
- Regard **medical patients** as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more **or**
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in **Box 1**.
- Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - one or more of the risk factors shown in **Box 1**.

Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (body mass index [BMI] over 30 kg/m^2)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in **Box 2,** unless the risk of VTE outweighs the risk of bleeding.

**At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH.*

Box 2 Risk factors for bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalized ratio [INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

- Reassess patients' risk of bleeding and VTE within 24 hours of admission, and whenever the clinical situation changes, to:
  - ensure that the methods of VTE prophylaxis used are suitable
  - ensure that VTE prophylaxis is being used correctly
  - identify adverse events resulting from VTE prophylaxis.

2.2.2 Reducing the risk of VTE – general recommendations

- Do not allow patients to become dehydrated unless clinically indicated.
- Encourage patients to mobilise as soon as possible.
- Do not regard aspirin or other antiplatelet agents as adequate prophylaxis for VTE.
- Consider offering temporary inferior vena caval filters to patients who are at very high risk of VTE (such as patients with a previous VTE event or an active malignancy) and for whom mechanical and pharmacological VTE prophylaxis are contraindicated.

2.2.3 Using VTE prophylaxis

2.2.3.1 Mechanical VTE prophylaxis

- Base the choice of mechanical VTE prophylaxis on individual patient factors including clinical condition, surgical procedure and patient preference. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

Anti-embolism stockings

- Do not offer anti-embolism stockings to patients who have:
  - 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 e.g. 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.

  Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers or wounds.

- Ensure that patients who need anti-embolism stockings have their legs measured and that the correct size of stocking is provided. Anti-embolism stockings should be fitted and patients shown how to use them by staff trained in their use.

- Ensure that patients who develop oedema or postoperative swelling have their legs re-measured and anti-embolism stockings refitted.

- If arterial disease is suspected, seek expert opinion before fitting anti-embolism stockings.

- Use anti-embolism stockings that provide graduated compression and produce a calf pressure of 14-15mmHg.

- Encourage patients to wear their anti-embolism stockings day and night until they no longer have significantly reduced mobility.

- Remove anti-embolism stockings daily for hygiene purposes and to inspect skin condition. In patients with a significant reduction in mobility, poor skin integrity or any sensory loss, inspect the skin two or three times per day, particularly over the heels and bony prominences.

- Discontinue the use of anti-embolism stockings if there is marking, blistering or discolouration of the skin, particularly over the heels and bony prominences or if the patient experiences pain or discomfort. If suitable, offer a foot impulse or intermittent pneumatic compression device as an alternative.

- Show patients how to use anti-embolism stockings correctly and ensure they understand that this will reduce their risk of developing VTE.

- Monitor the use of anti-embolism stockings and offer assistance if they are not being worn correctly.

Foot impulse devices and intermittent pneumatic compression devices

- Do not offer foot impulse or intermittent pneumatic compression devices to patients with a known allergy to the material of manufacture.

- Encourage patients on the ward who have foot impulse or intermittent pneumatic compression devices to use them for as much of the time as is possible and practical, both when in bed and when sitting in a chair.

2.2.3.2 Pharmacological VTE prophylaxis

- Base the choice of pharmacological agents on local policies and individual patient factors, including clinical condition (such as renal failure) and patient preferences.

2.2.4 Reducing the risk of VTE in medical patients

- Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE (see section 2.2.1). Choose any one of:

  - fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure).

  Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.*

Patients with stroke

- Do not offer anti-embolism stockings for VTE prophylaxis to patients who are admitted for stroke.

- Consider offering prophylactic-dose LMWH* (or UFH for patients with renal failure) if:

  - a diagnosis of haemorrhagic stroke has been excluded, **and**

  - the risk of bleeding (haemorrhagic transformation of stroke or bleeding into another site) is assessed to be low, **and**

  - the patient has one or more of:

    - major restriction of mobility

    - previous history of VTE

    - dehydration

    - comorbidities (such as malignant disease).

  Continue until the acute event is over and the patient's condition is stable.

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.*

- Until the patient can have pharmacological VTE prophylaxis, consider offering a foot impulse or intermittent pneumatic compression device.

Patients with cancer

- Offer pharmacological VTE prophylaxis to patients with cancer who are assessed to be at increased risk of VTE (see section 2.2.1). Choose any one of:

  - fondaparinux sodium

  - LMWH*

  - UFH (for patients with renal failure).

  Start pharmacological VTE prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented. LMWH.*

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant.

Patients with central venous catheters

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with central venous catheters who are ambulant.

- Consider offering pharmacological VTE prophylaxis with LMWH* (or UFH for patients with renal failure) to patients with central venous catheters who are at increased risk of VTE (See section 2.2.1).

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.*

Patients in palliative care

- Consider offering pharmacological VTE prophylaxis to patients in palliative care who have potentially reversible acute pathology. Take into account potential risks and benefits and the views of the patient and their family and/or carers. Choose any one of:

  - Fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure).

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.*

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients admitted for terminal care or those commenced on an end-of-life care pathway.

- Review decisions about VTE prophylaxis for patients in palliative care daily, taking into account the views of the patient, their family and/or carers and the multidisciplinary team.

Medical patients in whom pharmacological prophylaxis is contraindicated

- Consider offering mechanical VTE prophylaxis to **medical patients** in whom pharmacological prophylaxis is contraindicated. Choose any one of:

  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

2.2.5 Reducing the risk of VTE in surgical patients

2.2.5.1 General recommendations for all surgical patients

- Advise patients to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods.

- Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery. Consider involving the multidisciplinary team in the assessment.

- Consider regional anaesthesia for individual patients, in addition to other methods of VTE prophylaxis, as it carries a lower risk of VTE than general anaesthesia. Take into account the patients' preferences, their suitability for regional anaesthesia and any other planned method of VTE prophylaxis.

- If regional anaesthesia is used, plan the timing of pharmacological VTE prophylaxis to minimise the risk of epidural haematoma. If antiplatelet or anticoagulant agents are being used, or their use is planned, refer to the summary of product characteristics for guidance about the safety and timing of these in relation to the use of regional anaesthesia.

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients undergoing a surgical procedure with local anaesthesia by local infiltration with no limitation of mobility.

2.2.5.2 Recommendation for specific surgical patient groups

Cardiac surgery

- Offer VTE prophylaxis to patients undergoing **cardiac surgery** who are not having other anticoagulation therapy and are assessed to be at increased risk of VTE (see section 2.2.1)

  - Start mechanical VTE prophylaxis at admission. Choose any one of:

    - anti-embolism stockings (thigh or knee length)

    - foot impulse devices

    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

    - LMWH

    - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

Gastrointestinal, gynaecological, urological and thoracic surgery

- Offer VTE prophylaxis to patients undergoing **bariatric surgery**
  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length).

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
  - Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:
    - fondaparinux sodium
    - LMWH
    - UFH (for patients with renal failure).

    Continue pharmacological VTE prophylaxsis until the patient no longer has significantly reduced mobility (generally 5-7 days).
- Offer VTE prophylaxis to patients undergoing **gastrointestinal surgery** who are assessed to be at increased risk of VTE (see section 2.2.1)
  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length).

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
  - Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:
    - fondaparinux sodium
    - LMWH
    - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

- Offer VTE prophylaxis to patients undergoing **gynaecological, thoracic or urologic surgery** who are assessed to be at increased risk of VTE (see section 2.2.1)

  - Start mechanical VTE prophylaxis at admission. Choose any one of:

    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length).

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

    - LMWH
    - UFH (for patients with renal failure).

    Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

- Extend pharmacological prophylaxis to 28 days postoperatively for patients who have had major cancer surgery in the abdomen or pelvis.

Neurological (cranial or spinal)

- Offer VTE prophylaxis to patients undergoing **cranial or spinal surgery** who are assessed to be at increased risk of VTE (see section 2.2.1)

  - Start mechanical VTE prophylaxis from admission. Choose any one of:

    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length).

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

    - LMWH

- UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

- Do not offer pharmacological VTE prophylaxis to patients with ruptured cranial or spinal vascular malformations (for example, brain aneurysms) or acute traumatic or non-traumatic haemorrhage until the lesion has been secured or the condition is stable.

Orthopaedic- elective hip replacement

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing **elective hip replacement surgery**:

  - Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:

    - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)

    - foot impulse devices

    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:

    - dabigatran etexilate, starting 1-4 hours after surgery*

    - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established

    - LMWH, starting 6–12 hours after surgery

    - rivaroxaban, starting 6-10 hours after surgery$

    - UFH (for patients with renal failure), starting 6–12 hours after surgery.

    Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

** Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157(2008).*[476]

$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement

surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).[479]

Orthopaedic- elective knee replacement

Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing **elective knee replacement surgery**.

- Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:
  - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
- Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:
  - dabigatran etexilate, starting 1-4 hours after surgery*
  - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
  - LMWH, starting 6–12 hours after surgery
  - rivaroxaban, starting 6-10 hours after surgery$
  - UFH (for patients with renal failure), starting 6–12 hours after surgery.

  Continue pharmacological VTE prophylaxis for 10-14 days, according to the summary of product charateristics for the individual agent being used.

** Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157(2008).*[476]

$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).[479]

Orthopaedic- hip fracture

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing **hip fracture surgery**.

- Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:

  - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Provided there are no contraindications, add pharmacological VTE prophylaxis. Choose any one of:

  - fondaparinux sodium, starting 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see **Box 2**)
  - LMWH, starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.
  - UFH (for patients with renal failure), starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.

  Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

➢ Fondaparinux sodium is not recommended for use preoperatively for patients undergoing **hip fracture surgery**. If it has been used preoperatively it should be stopped 24 hours before surgery and started 6 hours after surgical closure, provided haemostasis has been established and there is no risk bleeding (see **Box 2**).

Other orthopaedic

➢ Consider offering combined VTE prophylaxis with mechanical and pharmacological methods to patients having **orthopaedic surgery (other than hip fracture, hip replacement or knee replacement)** based on an assessement of risks (see section 2.2.1) and after discussion with the patient. Start mechanical VTE prophylaxis at admission. Choose one of the following, based on individual patient factors:

  - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Start pharmacological VTE prophylaxis 6–12 hours after surgery. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Do not routinely offer VTE prophylaxis to patients undergoing **upper limb surgery**. If a patient is assessed to be at increased risk of VTE (see section 2.2.1) refer to recommendation for other orthopaedic surgery (above).

Vascular

- Offer VTE prophylaxis to patients undergoing **vascular surgery** who are not having other anticoagulant therapy and are assessed to be at increased risk of VTE (see section 2.2.1). If peripheral arterial disease is present, seek expert opinion before fitting anti-embolism stockings.
  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
  - Add pharmacological VTE prophylaxis for patients who have a low risk of bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
    - LMWH
    - UFH (for patients with renal failure).

    Continue pharmacological VTE prophylaxis until the patients no longer has significantly reduced mobility (generally 5-7 days).

Day surgery

- Offer VTE prophylaxis to patients undergoing **day surgery** who are assessed to be at increased risk of VTE (see section 2.2.1)
  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)

- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length).

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:
  - fondaparinux
  - LMWH
  - UFH (for patients with renal failure)

  If the patient is expected to have significantly reduced mobility after discharge, continue pharmacological VTE prophylaxis, generally for 5-7 days.

➢ Offer VTE prophylaxis to patients undergoing surgery **other than that covered in section 2.2.5.2** who are assessed to be at increased risk of VTE (see recommendation 2.2.1).

- Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

2.2.6 Other patient groups

Major trauma

➢ Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients with **major trauma**. Regularly reassess the patient's risks of VTE and bleeding.

- Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:

    - anti-embolism stockings (thigh or knee length) used with caution (see section 2.2.3.1)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see **Box 2**) and the bleeding risk has been established as low, add pharmacological VTE prophylaxis and continue until the patient no longer has significantly reduced mobility. Choose one of:

    - LMWH
    - UFH (for patients with renal failure).

    Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

Spinal injury

- Offer combined VTE prophylaxis with mechanical and pharmacological methods tor patients with spinal injury. Regularly reassess the patient's risks of VTE and bleeding.

    - Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:

        - anti-embolism stockings (thigh or knee length) used with caution (see section 2.2.3.1)
        - foot impulse devices
        - intermittent pneumatic compression devices (thigh or knee length)

        Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility

    - If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see **Box 2**) and the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:

        - LMWH
        - UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility

Lower limb plaster casts

- Consider offering pharmacological VTE prophylaxis for patients with lower limb plaster casts after evaluating the risks (see section 2.2.1) and benefits based on clinical discussion with the patient. Offer LMWH (or UFH for patients with renal failure) until lower limb plaster cast removal.

Pregnancy and up to 6 weeks post partum

- Consider offering VTE prophylaxis with LMWH (or UFH for patients with renal failure) to women who are **pregnant or have given birth within the previous 6 weeks who are admitted to hospital but are not undergoing surgery** and have one or more of the following risk factors:
    - expected to have significantly reduced mobility for 3 or more days
    - active cancer or cancer treatment
    - age over 35 years
    - critical care admission
    - dehydration
    - excess blood loss or blood transfusion
    - known thrombophilias
    - obesity (pre-pregnancy or early pregnancy BMI over 30 kg/m^2)
    - one or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
    - personal or a first degree relative with a history of VTE
    - pregnancy related risk factor (such as ovarian hyperstimulation, hyperemesis gravidarum, multiple pregnancy and pre-eclampsia)
    - varicose veins with phlebitis.
- Consider offering combined VTE prophylaxis with mechanical methods and LMWH (or UFH for patients with renal failure) to women who are **pregnant or have given birth within the previous 6 weeks who are undergoing surgery**, including caesarean section.
- Offer mechanical and/or pharmacological VTE prophylaxis to women who are **pregnant or have given birth within the previous 6 weeks** only after assessing the risks and benefits and discussing these with the patient and with healthcare professionals who have knowledge of the proposed method of VTE prophylaxis

during pregnancy and post partum. Plan when to start and stop pharmacological VTE prophylaxis to minimise the risk of bleeding.

Critical Care

- Assess all patients on admission to the **critical care** unit for their risks of VTE (see section 2.2.1) and bleeding (see **Box 2**). Reassess patients' risks of VTE and bleeding daily and more frequently if their condition is changing rapidly.

- Offer VTE prophylaxis to patients admitted to the critical care unit based on the reason for admission, taking into account:

    - any planned interventions

    - the use of other therapies that may increase the risk of complications.

- Review decisions about VTE prophylaxis for patients in **critical care** daily and more frequently if their condition is changing rapidly. Take into account the known views of the patient, comments from their family and/or carers and the multidisciplinary team.

Patients already having antiplatelet agents or anticoagulants on admission or needing them for treatment

- Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 2.2.1). Take into account the risk of bleeding (see **Box 2**) and of comorbidities such as arterial thrombosis.

    - If the risk of VTE outweighs the risk of bleeding, consider offering pharmacological VTE prophylaxis according to the reason for admission.

    - If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis.

- Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are taking vitamin K antagonists and who are within their therapeutic range, providing anticoagulant therapy is continued.

- Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH).

2.2.7 Patient information and planning for discharge

Patient information

- 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.

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

- Before starting VTE prophylaxis, offer patients and/or their families or carers verbal and written information on:
    - the risks and possible consequences of VTE
    - the importance of VTE prophylaxis and its possible side effects
    - the correct use of VTE prophylaxis (for example, anti-embolism stockings, foot impulse or intermittent pneumatic compression devices).
    - how patients can reduce their risk of VTE (such as keeping well hydrated and, if possible exercising and becoming more mobile)

Planning for discharge

- As part of the discharge plan, offer patients and/or their families or carers verbal and written information on:
    - the signs and symptoms of deep vein thrombosis and pulmonary embolism
    - the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)
    - the importance of using VTE prophylaxis correctly and continuing treatment for the recommended duration (if discharged with prophylaxis)
    - the signs and symptoms of adverse events related to VTE prophylaxis (if discharged with prophylaxis)
    - the importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis)
    - the importance of seeking medical help if deep vein thrombosis, pulmonary embolism or other adverse events are suspected.
- Ensure that patients who are discharged with anti-embolism 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.

- Ensure that patients who are discharged with pharmacological and/or mechanical VTE prophylaxis are able to use it correctly, or have arrangements made for someone to be available who will be able to help them.

- Notify the patient's GP if the patient has been discharged with pharmacological and/or mechanical VTE prophylaxis to be used at home.

2.3 Recommendations for research

2.3.1 Assessment of risk for VTE

The Guideline Development Group (GDG) recommended the following research question:

- What is the absolute risk of VTE among different groups of hospital patients and can the risk be reliably estimated on admission to hospital to ensure that appropriate patients are offered VTE prophylaxis?

Why this is important

One of the most difficult areas the Guideline Development Group faced when developing the guideline was to identify the absolute risk of VTE among specific patient groups in relation to the reason for admission. A new, large pragmatic cohort study and/or record linkage study using Hospital Episode Statistics and the General Practice Research Database is proposed. This would allow all people admitted to hospital to be studied to identify those who develop VTE, including people who are diagnosed with VTE in primary care after discharge from hospital. Information on baseline patient-related factors, procedures and duration of stay, complications, prophylactic therapies and concomitant drug use should be collected and analysed. It should allow the identification of independent risk factors for VTE and the development and subsequent validation of a risk model to estimate the absolute risk of VTE in individual patients. This research would allow clearer identification of those patients at risk of VTE and those in whom the risk is so low that the bleeding risk of pharmacological VTE prophylaxis would add overall hazard.

2.3.2 VTE prophylaxis for general medical patients

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of pharmacological prophylaxis, mechanical prophylaxis and combined pharmacological and mechanical prophylaxis for reducing the risk of VTE in medical patients?

Why this is important

Only a small number of trials with medical patients were identified and generally the inclusion criteria were narrow, for example, patients with an acute medical illness, with a hospital stay of more than 5 days, and often with severely limited mobility. Further research into less severely ill patient groups would be beneficial.
The evidence concerning mechanical prophylaxis in medical patients is sparse. There have been a few small trials of patients with coronary syndrome but the only large,

randomised controlled trial was of patients with stroke. This trial showed that routine care plus thigh-length anti-embolism stockings did not confer significantly more protection against VTE than routine care alone and was associated with significantly more harm. All of these trials included large proportions of patients who were taking aspirin, which may have influenced the results.
New trial(s) should investigate the benefits of reducing the risk of VTE balanced against the risk of bleeding. The trial(s) should compare pharmacological prophylaxis alone, mechanical prophylaxis alone, and combined mechanical and pharmacological prophylaxis. The benefit of extended-duration prophylaxis in medical patient groups may also be investigated.

2.3.3 VTE prophylaxis for patients with lower limb plaster casts

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of pharmacological prophylaxis for reducing the risk of VTE in patients with lower limb plaster casts?

Why this is important

A number of randomised controlled trials have been published reporting the use of VTE prophylaxis in patients with lower limb plaster casts. However, within these trials there has been a range of patients including patients with soft tissue injuries and no operation, those with operated and unoperated fractures and patients having elective procedures. The incidence of VTE in the published trials that did not use VTE prophylaxis ranges from 4%–40%. The implications of providing pharmacological prophylaxis for all patients with lower limb plaster casts are potentially considerable with respect to cost. Trials stratifying patients by reason for plaster cast would be useful to determine which patients should be recommended for prophylaxis.

2.3.4 VTE prophylaxis for patients after stroke

The GDG recommended the following research question:

- What is the overall risk/benefit of low molecular weight heparin and/or fondaparinux sodium in respect of both stroke outcome and the development of VTE for patients with acute stroke?

Why this is important

Patients with either ischaemic or haemorrhagic stroke have a risk of both VTE and bleeding into the brain. 'Stroke: diagnosis and management of acute stroke and transient attack [TIA]' (NICE clinical guideline 68, published July 2008) recommends the use of aspirin for treatment of ischaemic stroke but does not recommend anticoagulants. There is recent evidence to suggest that prophylactic-doses of anticoagulants in addition to aspirin reduce the risk of VTE in patients with ischaemic stroke but there are no data showing an effect of these anticoagulants on the stroke itself. Do they increase the risk of haemorrhagic transformation and so increase neurological damage? This research should include patients with haemorrhagic or ischaemic strokes to identify which patients would benefit from additional pharmacological prophylaxis.

2.3.5 Incidence of post-thrombotic syndrome after venous thromboembolism

The GDG recommended the following research question:

- What is the incidence, loss of quality of life and cost associated with post-thrombotic syndrome after potentially preventable deep vein thrombosis?

Why this is important

During development of the guideline it became apparent that the incidence of post-thrombotic syndrome, particularly after asymptomatic deep vein thrombosis, was not well reported. This study should use standard, validated definitions to identify the incidence of post-thrombotic syndrome both when a deep vein thrombosis has occurred as a result of a hospital admission and in the absence of hospital-acquired deep vein thrombosis. The study also should aim to identify the costs to the NHS of treating post-thrombotic syndrome.

5 Risk, risk reduction and harm

5.1 Introduction

In making a judgement on the use of an intervention to reduce the risk of VTE, it is important to consider:

i. the reason for admission to hospital (e.g. a surgical procedure or a medical problem) and factors individual to the patient concerned (e.g. age, gender, pre-existing medical conditions and medication use) that influence the likelihood of VTE

ii. the likely treatment benefit from the specific prophylactic intervention

iii. the possible harmful effect of the intervention (e.g. bleeding from the use of pharmacological VTE prophylaxis).

While clinicians are used to evaluating these factors in a qualitative sense, the Guideline Development Group sought to obtain quantitative information where possible. The risk of VTE, risk reduction with a prophylactic intervention and risk of harm can all be expressed in absolute or relative terms. In some guidelines, patient related risk factors are expressed in relative terms. For example, patients with a prior history of VTE undergoing a surgical procedure were estimated to have an approximately 5-fold higher relative risk of DVT than patients with no such history (section 5.7.3). The current CMO risk assessment tool[163] does not try to quantify the risks.

However, in balancing benefit and harms in an individual patient, it can be more helpful to consider risk in absolute terms. For example, if the absolute risk of VTE during hospitalisation is 10% (i.e. a there is a 1 in 10 chance of VTE), and pharmacological prophylaxis reduces this risk by one half (i.e. a relative risk reduction of 50%), the absolute reduction risk from the intervention would be 5%. In simple terms, this means that there would be 5 fewer VTE events during hospitalisation in every 100 such patients treated, or 1 fewer event for every 20 treated (number needed to treat [NNT]=20). In a lower risk group of patients where the absolute risk of VTE is 1% (i.e. a 1 in 100 chance of VTE during hospitalisation) but the same intervention continues to reduce VTE risk by one half (i.e. the same relative risk reduction), the reduction in absolute risk of VTE would be only 0.5% (NNT=200). If the intervention doubles the risk of major bleeding from 0.5% to 1% in both situations (number needed to harm [NNH]=200), it might be considered to be helpful in the first group of patients but not the second.

5.2 Sources of information on risks, risk reduction and harm

Estimates of effect of treatment are obtained from randomised controlled trials (RCTs). Absolute risk reductions are readily calculated from data in individual RCTs, but meta-analysis of trial data, conducted to encompass the totality of evidence, conventionally generates a pooled estimate of the relative (rather than absolute) risk reduction. This is to overcome the problem that patients studied in different trials of the same intervention can have differing baseline absolute risk of VTE. A clinician may estimate the absolute risk reduction expected from an intervention by simply multiplying the pooled estimate of the relative risk reduction by the absolute risk of VTE in the patient group being considered. This requires reliable information on the absolute risk of VTE in different settings. However, the Guideline Development Group noted that information on the absolute risk of VTE in various clinical situations was limited. Three sources of information were considered:

(i) randomised controlled trials themselves

(ii) registries of routinely collected clinical data (e.g. Hospital Episode Statistics and the General Practice Research Database)

(iii) prospective cohort (incidence) studies

Because both the risk of VTE and the harms from treatment (particularly major bleeding) could differ substantially, information on absolute risks and harms in medical and surgical admission settings were considered separately.

5.3 Absolute risk of VTE during surgical admission

To assess absolute risk of VTE during a surgical admission or soon after, we have extracted data from three sources:

a) randomised controlled trials

b) registries of routinely collected clinical data

c) prospective cohort studies.

5.3.1 Evidence from randomised controlled trials

For these analyses, RCTs were grouped according to types of surgery using categories agreed by consensus within the guideline development group responsible for the development of the surgical guideline. Within each category, the total number of DVT events, the total number of symptomatic PE events and the total number of patients in the control (no prophylaxis arms) of RCTs were recorded. Studies were excluded if they reported any form of background prophylaxis other than early mobilisation. However, some patients may have had off-protocol prophylaxis at the discretion of their physicians. Studies were only included if they scanned all patients to find DVT (including asymptomatic DVT). This will result in the incidence figures reported being higher than the figures generally identified in practise which are usually only symptomatic events.

A pooled estimate of the absolute risk of any (including asymptomatic) DVT, and symptomatic pulmonary embolism (PE) was estimated by a fixed effects meta-analysis, which used a Freeman-Tukey arcsine transformation to stabilise the variances of the individual study proportions [446] (Table 5-17). The types of surgery with the highest risk

of DVT and symptomatic PE were (major) orthopaedic surgery followed by (major) general surgery and then neurosurgery.

The strengths of this source of information is that the patients are being carefully followed, ensuring that disease endpoints are unlikely to have been missed. In addition it is known in the control arms of the RCTs, no intervention was used, providing an estimate of absolute risk in the absence of any treatment. Finally it is known that the diagnosis of VTE was confirmed by appropriate imaging tests. However, the limitation is that patients studied in RCTs may not adequately represent the full spectrum of patients encountered in clinical practice which may limit the ability to generalise the findings. Furthermore, for some categories of surgery the available sample size was small.

Table 5-17: Risk of DVT and pulmonary embolism by type of surgery, from the no prophylaxis arm of RCTs

	Number of patients with an event	*Sample Size*	*Incidence*	*Incidence Lower 95% CL*	*Incidence Upper 95% CL*
DVT					
Cardiac [41,345]	10	65	14%	7%	24%
General [5,13,53,65,88,89,97,112,171,230,238,239,279,289,371,372,385,405,423,498,499,528,550,552,553,560,590,593,594,625,641,643,653,703,711,716]	569	2286	24%	23%	26%
Gynaecology [30,73,113,114,117,414,530,633,644,682]	113	691	16%	13%	19%
Neurological [90,101,441,607,646,647,649,683]	91	446	20%	17%	24%
Orthopaedic (Elective Hip) [12,39,51,151,153,189,207,209,249,261,281,296,301,380,410,433,587,638,650,659,684,705]	530	1172	45%	42%	48%
Orthopaedic (Hip fracture) [74,176,185,209,248,268,312,316,370,381,385,463,464,470,533,613,631,704,710]	471	1139	40%	37%	43%
Orthopaedic (Elective knee) [291,388,436,443,697,699]	65	108	60%	51%	69%
Orthopaedic Mixed [7,27,69,290,521,700]	66	140	47%	39%	55%
Urological [119,266,267,386,668]	18	144	10%	6%	15%
Vascular [615]	2	19			
Mixed [21,54,111,115,166,208,209,284,302,326,416,585,629]	286	1303	22%	19%	24%
Not known [93,337,360,364,718]	102	276	36%	31%	42%
All	2353	8089	29%		
Symptomatic Pulmonary Embolism					
Cardiac	0	0			
General [5,238,280,372,373,405,499,517,552,653]	72	3044	1%	1%	2%
Gynaecology [113,114,117]	2	250	1%	0%	3%
Neurological [607,649]	0	129			
Orthopaedic (Elective Hip) [12,51,261,281,296,410,433,587,612,638,650,684,705]	32	760	3%	2%	5%

Orthopaedic (Hip fracture)[74,176,178,185,381,463,464,470,533]	63	811	8%	6%	10%
Orthopaedic (Elective Knee)[697]	0	32			
Orthopaedic Mixed[27,695]	23	134	19%	13%	25%
Urological[40,119]	2	41	9%	3%	19%
Vascular[615]	0	19			
Mixed[284,344]	7	711	1%	1%	2%
Not known	0	0			
All	175	5723	3%		

5.3.2 Evidence from clinical registry data

Hospital Episode Statistics

The NHS Hospital Episode Statistics database holds data on every patient admitted to an NHS hospital in England. We extracted data from the year 2003/4. This section has been incorporated from the previous surgical guideline[473] and has not been updated as part of the development of this guideline.

We identified all patients with a secondary diagnosis of symptomatic DVT or pulmonary embolism (ICD10=I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82.1, I82.2, I82.8, I82.9) but excluded those that had not been admitted for surgery. We generated categories of surgical treatment by consensus. We then calculated the incidence of VTE for each surgical procedure using the total number of procedures performed over the same period as the denominator.

Table 5-18 shows the different surgical categories in order of the incidence of symptomatic VTE. The types of surgery with the highest risk of VTE are cardiothoracic, major orthopaedic and vascular surgery followed by major abdominal general surgery.

The advantage of this type of data is that they better reflects the spectrum of patients encountered in everyday practice. The disadvantages include the possibility that the diagnosis of VTE may have been inaccurate in some cases, the recording and coding of VTE may have been incomplete, and the absolute risks may not be directly comparable across categories because of the varying lengths of stay involved with different surgical interventions. Moreover, the estimates of absolute risk reflect may not be directly comparable with estimates made using data from the control arm of clinical trials because many patients in the HES registry will have received some form of thromboprophylaxis. Table 5-18 shows this incidence of symptomatic VTE by type of surgery, as recorded in HES.

Table 5-18: Incidence of symptomatic VTE estimated from HES 2003/4

	Number of patients with an event	*Sample Size*	*Incidence*
Femoral head	237	23538	1.01%
Knee replacement	493	52535	0.94%

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

US clinical registry data

White et al. (2003)[690] evaluated the incidence of symptomatic VTEs in a database of 1.7 million patients in 76 surgical categories in the USA. They included cases of symptomatic VTE occurring during either the initial hospitalisation or a subsequent hospitalisation within 91 days of the surgery. Procedures in patients without a diagnosis of cancer where the risk of VTE was greater than 2% were:

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

Among patients with cancer, surgical procedures where the absolute risk of symptomatic VTE was greater than 2% were:

- Permanent colostomy 2.6%
- Radical cystectomy 3.7%
- Percutaneous nephrostomy 3.6%

- Exploratory laparotomy 2.4%
- Internal fixation of femur 3.0%

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

5.3.3 Prospective cohort studies

This section has been incorporated from the previous surgical guideline[473] and has not been updated as part of the development of this guideline.

The sixteen other studies found[19,25,63,187,230,288,309,334,428,432,461,518,566,604,652,677] were difficult to summarise, because of their heterogeneity, but if we compare the incidence rates with those in Table 2, it would seem that there is a relatively high risk of VTE associated with prostatectomy, gynae-oncological surgery and neurosurgery and a low risk associated with surgery for breast cancer or head and neck/ENT surgery (Evidence Table 1, Appendix D).

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

5.3.4 Discussion of data on surgical risk

We used different sources to estimate the risk of VTE for different categories of surgery compared with other surgery types. The incidence figures for VTE estimated using HES data were much lower than other estimates, implying under-reporting and/or treatment in the community. This was true even when compared to a similar database in the USA[690]. The figures for DVT from the 'no prophylaxis' arms of the RCTs appears higher than other estimates due to the identification of asymptomatic DVT events by screening the legs, as well as symptomatic events.

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

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

The differences in incidence within the broad surgical categories are probably much greater than the differences between categories[690].

The strategy that the Guideline Development Group adopted from this evidence was to consider major orthopaedic surgery as higher risk for VTE than cardiac, thoracic, urological, vascular, gynaecological, neurological and general surgery. Within

orthopaedic surgery, hip fracture was considered to be highest risk followed by elective orthopaedic procedures and then other types of major orthopaedic surgery.

The surgical guideline development group decided that the no-prophylaxis arms of the RCTs was the best source for the baseline risk of VTE and major bleeding, and this was used in our cost-effectiveness analysis (Chapter 4). The advantage of these risk estimates is that they control for prophylaxis use. However, the Guideline Development Group acknowledged also the weaknesses in these data. Firstly trial populations might not be representative of surgical patients in general. Second, it has been postulated that the incidence of VTE has fallen over time due to prophylaxis use but also due to other factors. If this is true then the RCT evidence, which goes back to the 1970s may over-estimate the risk of DVT and PE. Conversely, since RCT protocols usually involve surveillance for asymptomatic DVT, they might under-estimate the incidence of PE if DVTs are being diagnosed and actively before the time when they would have become symptomatic in a non-trial setting.

5.4 Absolute risk of VTE during medical admissions

We obtained information on the absolute risk of VTE during a medical admission from:

a) randomised controlled trials

b) incidence studies

5.4.1 Evidence from randomised controlled trials

The incidence of all (including asymptomatic) DVT and symptomatic PE was estimated from the RCTs in our clinical review were extracted and analysed as per the methodology as detailed in Section 5.3. These data are presented in Table 5-19.

Table 5-19: Risk of DVT and symptomatic PE, by medical condition, from the nil arm of RCTs

	Number of patients with an event	*Sample Size*	*Incidence*	*Incidence Lower 95% CL*	*Incidence Upper 95% CL*
DVT					
General Medical Patients[121,141,191,579]	106	827	13%	11%	15%
Stroke [157,167,240,434,435,520,538,540,581]	195	384	50%	45%	55%
Acute Coronary Syndromes[42,209,251,252,338,522,672,709]	76	372	21%	17%	25%
All	377	1583	24%		
Symptomatic Pulmonary Embolism					
General Medical Patients[121,394,579]	24	2400	0.9%	0.6%	1.3%
Stroke [157,520]	2	54	3%	0%	9%
Acute Coronary Syndromes[42,251,445,709]	5	156	4%	2%	8%
All	17	2638	1%		

Alongside the limitations of using RCT data to determine the incidence of DVT as detailed in section 5.3.1 the studies reporting on 'general medical patients' included a range of different medical conditions. Therefore some studies included in this population will have ischaemic stroke or acute coronary syndromes, but it was not possible to identify these separately.

5.4.2 Incidence studies

A search was conducted to identify primary studies reporting the incidence of VTE in medical patients. The Guideline Development Group were concerned that the incidence of VTE may have changed over time due to advances in medical practice and so a time limit was put on the search to only find papers published from 1998 – 2008. After the review and data extraction of some of thse studies (Evidence Table 2, Appendix D) it became apparent that similar problems as those detailed in section 5.3.2 were being encountered and the information provided was not as useful as had been hoped. The studies reviewed differed in the methods used, populations included, outcomes measured and confounding factors considered, particularly the use of VTE prophylaxis. These factors meant that the comparison of the results between studies was not possible. Once this had been identified as a problem, no further papers were reviewed and the results as presented below are used to demonstrate the inconsistency of these data.

Eighteen (18) studies were reviewed, 6 of these studies were database reviews [67,68,241,606,623,624] whereas 12 were cohort studies [77,134,144,149,173,320,349,453,469,501,512,567] (Evidence Table 2, Appendix D).

The larger studies looking across all hospital admissions used database coding in order to identify VTE which may not capture all events, particularly those occurring after discharge. In addition, most database reviews do not provide details on any VTE prophylaxis, which is likely to be because the prophylaxis strategy was not recorded in the database and may have differed across departments and/or hospitals.

Data from registries

One database review found that the incidence of symptomatic PE in stroke patients[606] (0.51% for ischaemic stroke and 0.68% for haemorrhagic stroke) and in patients admitted with cancer patients[623] (0.6%) were greater that the symptomatic PE rate across all patients admitted to hospital[624] (0.23% [95% CI: 0.21 – 0.25%]) which included medical, surgical and trauma patients.

Cohort studies

Cohort studies specifically for critical care patients (usually including surgical patients) [134,320,512], acute exacerbation of COPD[173], ischaemic stroke[149], congestive heart failure[144] and rehabilitation units[567] were reviewed (Evidence Table 2, Appendix D).

5.5 Absolute risk of major bleeding after surgery

The relative risk increases for major bleeding from pharmacological prophylaxis after surgery are outlined in chapters 9-18. The current section summarises evidence on the absolute risk of bleeding after different surgery.

The absolute risk of bleeding after surgery is even more difficult to find than the absolute risk of VTE. The main source of information that was used to establish the baseline risks of major bleeding in this population were the nil prophylaxis arms of RCTs.

These data from individual trials were combined using a meta-analysis technique as described in section 5.3.1.

Use of evidence for major bleeding incidence from RCTs has limitations as although many of the newer studies may use a fairly standard definition of major bleeding. A major bleeding event is defined as a bleeding event that results in one or more of the following: death; a decrease in haemoglobin concentration of 2g/dl or more; transfusion of at least 2 units of blood; bleeding from a retroperitoneal; intracranial; or intraocular site; a serious or life-threatening clinical event; a surgical or medical intervention. Some studies have modified this definition and others use their own trial specific definition. The Guideline Development Group agreed to use the definition of major bleeding as reported in the trials.

Another major limitation of using the absolute bleeding risk from RCTs is that they are likely to have excluded patients at increased risk of bleeding and so the incidence reported may be an underestimate of the total population.

We are not aware of any prospective cohort studies that investigate the absolute risk of bleeding after surgery in the absence of prophylaxis. Many of the definitions may not include the 'minor' bleeding which can cause serious wound complications which can be associated with a considerable loss of quality of life and cost.

Table 5-20: Risk of major bleeding, by type of surgery, from the nil arm of RCTs

	Number of patients with an event	*Sample Size*	*Incidence*	*Incidence Lower 95% CL*	*Incidence Upper 95% CL*
Major Bleeding					
Cardiac[41]	1	25			
General[5,29,53,172,230,238,280,289,319,366,371,385,499,511,517,528,550,553,590,639,653,703,711,716]	83	3980	2%	1%	2%
Gynaecology[113,414,530,633,682]	13	306	4%	2%	7%
Neurological[101,441]	1	113	2%	0%	5%
Orthopaedic (Elective Hip)[12,39,151,153,249,261,380,410,421,587,650,659,684]	25	117	2%	1%	2%
Orthopaedic (Hip fracture)[74,176,178,248,312,316,381,385,463,464,533,704,710]	29	772	3%	2%	5%
Orthopaedic (Elective knee)[388,436,443,699]	4	274	2%	1%	4%
Orthopaedic (Mixed) [7,69,521,700]	0	58			
Urological[14,40,267,386,668]	2	170	2%	0%	4%
Vascular [615]	0	19			
Mixed[54,111,166,326,344,569]	2	1153	0%	0%	0%
Not known[93,337,364,365,718]	2	254	1%	0%	3%
All	167	7241	2%		

The absolute risk of major bleeding rate for most surgery was between 1-2% as reported in the trials, although the Guideline Development Group noted that gynaecological surgery had a higher risk of major bleeding at 4%.

5.6 Absolute risk of major bleeding after medical admissions

The relative risk increases for major bleeding from pharmacological prophylaxis are outlined in chapters 23 to 25. The current section summarises evidence on the absolute risk of bleeding in different settings.

The same method as in section 5.5 was used to identify the absolute risk of bleeding in patients admitted for medical conditions. The incidence of bleeding in the general medical population appeared to be lower than the risk of bleeding after stroke.

Table 5-21: Risk of major bleeding, by medical condition, from the nil arm of RCTs

	Number of patients with an event	*Sample Size*	*Incidence*	*Incidence Lower 95% CL*	*Incidence Upper 95% CL*
Major Bleeding					
General Medical Patients[121,191,394,579]	11	2629	0.4%	0.2%	0.7%
Stroke[167,540,581]	4	107	4%	1%	9%
Acute Coronary Syndromes[70]	0	14	Not Estimable		
All	15	2750	0.6%		

5.7 Individual patient risk factors and relative risks of VTE

Published risk assessment tools

No existing, published risk assessment tools have been recommended because the literature search did not identify any that have been validated in a broad range of patients and been shown to improve patient outcomes. The Department of Health published a risk assessment tool in September 2008[163] and it is intended that this tool will be updated at the time of publication of the NICE guideline to ensure that the wording is consistent.

Search for inidivdual patient risk factors

Because risk factors specific to the patient may modify absolute risk in any setting we searched for systematic reviews on patient related risk factors for DVT or PE. For the previous guideline, the search was confined to patients admitted for surgical procedures. We identified one study that included several systematic reviews encompassing various risk factors in surgical patients[169]. The search was extended to any patient group exposed to a risk factor when insufficient information was found in surgical populations. Several reviews were identified for non-surgical populations[24,156,206,336,444,562,580].

Some reviews only included studies that used an objective test for diagnosing venous thromboembolism such as a fibrinogen uptake or ultrasound, whereas others did not report the method of diagnosis for studies included. The number of cases and controls was not always reported. Details for each systematic review are reported below. We

also referred to previous guidelines for their included risk factors[219,591]. The search for individual patient risk factors for VTE in surgical patients was not updated as part of the development of this guideline. Results have been incorporated from the previous surgical guideline [473].

For the current guideline we developed and ran a search to look for any recent systematic reviews of risk factors for hospitalised medical patients (Appendix C). One systematic review of VTE risk factors in hospitalised medical patients was found[556]. Although the paper appears to have completed a systematic search of the literature, limitations include that details of the individual studies included such as the populations and number of patients within the study, is not always presented and the definition of VTE of the method for its detection was often not clear. In addition no pooling of risk was attempted in this paper making an overall summary of the results difficult.

For each risk factor, information is reported in relative rather than absolute terms (using relative risks or odds ratios). One way in which clinicians might use this information is to scale up absolute risk derived from the sources listed above in a patient with one of the risk factors listed below. For example a patient with a prior history of DVT undergoing a surgical procedure where the absolute risk of DVT is 1% on average might be expected to have personal absolute risk of 5%. However, in patients with more than one risk factor, risks are unlikely to simply be multiplicative because many individual risk factors are unlikely to be independent. For this reason, the Guideline Development Group recommends new prospective cohort studies of hospitalised patients be conducted for the development and validation of a multivariable risk models for the estimation of absolute risk of DVT in individual patients, that could be applied in the clinical setting (section 5.10).

5.7.1 Age

Edmonds et al [169] identified six studies investigating the association between age and postoperative DVT (evidence level 2+). There was a general trend of increased age being associated with an increased risk of DVT in all studies. Two of the studies showed the incidence of DVT to be higher in those over 60 than those under; two studies showed the mean age of patients with DVT to be higher than those without DVT; and two studies showed an incremental increase associated with increasing age, one of them finding the risk to be constant at below 45 years of age. A pooled risk estimate was not possible because of the different ways of investigating across the studies (Evidence Table 3, Appendix D).

Rocha et al[556] identified a further 5 studies, 3 of which were conducted in the general population and the remaining 2 in medical inpatients (evidence level 2+). All studies confirmed a significant increase in VTE risk with increasing age although cut offs were different for each study (cut offs ranged from 50 to 85 years) (Evidence Table 3, Appendix D).

Although the increased risk of DVT with increasing age has been demonstrated by many studies and is relatively uncontroversial, it is difficult to provide useful guidance without providing a cut-off at which a person should be considered at 'increased risk'. There is no universally agreed figure for this cut off. Some guidelines have put an age threshold of 40 although White et al[688] found that the relationship between age, type of surgery and risk is complex, in particular there is no evident step up in risk at 40. Anderson & Spencer[17] noted stratification of risk by the simple dichotomy of age below or above 40 years fails to account for the significantly higher risk among the elderly patients undergoing high risk surgical procedures.

The guideline development group agreed that an age cut off of 60 years should be used. In addition to the evidence detailled above, the decision was also made based on the patients included in the trials. The patients included in the studies for general surgery patients (and therefore included in our cost effectiveness model) had average age of 60 years (chapter 9). It was the decision of the guideline development group that setting an age cut off lower than age 60 may lead to the provision of VTE prophylaxis unnecessarily where no other risk factors were present which could lead to greater harm than benefit.

Although the average age of patients included in VTE prophylaxis trials of medical patients (74 years) was greater than for general surgery trials it was noted that in the recommendation for medical patients both reduced mobility and an age over 60 years was required in order for prophylaxis to be offered.

5.7.2 Obesity

Edmonds et al. [169] identified seven studies investigating the association between obesity and postoperative DVT (evidence level 2+). Five out of the seven studies found a significant association between an increase in obesity and risk of DVT and two found no significant difference. A pooled estimate was not possible because of different definitions for obesity used across the studies (Evidence Table 4, Appendix D).

Rocha et al[556] identified a further nine studies, although the definitions of VTE and of obesity used were unclear within the review (evidence level 2+). Three studies reported that they found no evidence of a correlation between obesity and VTE whereas five studies reported a significant increase in VTE risk (between 2.0 and 3.92). The remaining study found a large VTE relative risk increase (RR rose from 2 to 10) for obese patients using hormonal contraceptives (Evidence Table 4, Appendix D).

We used the definition of obesity as being patients with a body mass index greater than or equal to 30 kg/m^2 which is the definition used in the current NICE guidelines[474].

5.7.3 Personal or family history of VTE

Edmonds et al[169] identified four studies investigating the association between a history of venous thrombosis and postoperative DVT (evidence level 2+). When three of the studies were pooled, they indicated a significant association between past history of venous thrombosis and risk of DVT (OR=5.18, 95% CI: 3.16 to 8.49). The other study suggested no difference but did not provide any data (Evidence Table 5, Appendix D).

Rocha et al.[556] identified six studies in medical patients and the general population (evidence level 2+); four of which were case control reports and the remaining two were cohort studies. All of these studies identified a significant association between a history or previous VTE and a risk of future VTE events. No pooling of events was completed (Evidence Table 5, Appendix D).

In addition to a personal history of VTE, the GDG felt it was important to ask about any family history of previous VTE events in first degree relatives during the risk assessment. In this way it may be possible to identify patients who are at risk of inherited thrombophilias that may remain undiagnosed at the time of admission.

5.7.4 Known thrombophilias

Thrombophilias are the genetic or acquired prothrombotic states that increase the tendency to venous thromboembolism (Evidence Table 6, Appendix D).

Edmonds et al[169] identified two studies investigating the association between activated protein C (APC) resistance or Factor V Leiden (FVL) mutation and postoperative DVT (evidence level 2+). One study reported low sensitivity to APC was shown to be significantly associated with postoperative DVT (RR=4.9, 95% CI: 1.1 to 22.2) with 95% of the cases being attributable to the FVL mutation. The second study reported that a low sensitivity of FVL to APC (OR=2.97, 95% CI: 1.27 to 6.92) and FVL mutation (OR=3.18, 95% CI: 0.99 to 10.2) were associated with postoperative DVT.

Rocha et al.[556] identified nine studies investigating the impact of FVL mutation and VTE (evidence level 2+). The increase in relative risk reported ranged from 2.2 to 6.6 although no pooling was attempted. Five studies reported the impact of protein C deficiency on VTE and the increase in relative risk ranged from 3.4 to 7.3. (Evidence Table 6, Appendix D). These results support the findings in surgical patients.

Two of the studies included in the review by Edmonds et al.[169] examined antithrombin deficiency (evidence level 2+). One found patients who developed postoperative DVT had a lower level of antithrombin, the other did not find any association. We also identified one systematic review that looked at deficiency in antithrombin, protein C or protein S463. All three were associated with an increased risk of postoperative venous thromboembolism with relative risks of 5, 6.5 and 1.7 respectively. No information was given as to how venous thrombosis was diagnosed. Edmonds et al.[169] found no surgical studies investigating other thrombophilias.

Rocha et al.[556] identified 3 studies investigating anti-thrombin III deficiency (evidence level 2+). These studies all found an increased risk of VTE with the deficiency with the odds ratio varying between 1.7 and 12.6 in the studies (Evidence Table 6, Appendix D).

One additional thrombophilia investigated in the systematic review by Rocha et al. [556] was protein S deficiency. Four papers investigating the risk of VTE with protein S deficiency found that it increased the odds ratio for VTE between 0.7 and 14.4.

We identified one systematic review with 25 studies that looked at the association for lupus anticoagulants and/or anticardiolipin with thrombosis (venous or arterial) in medical populations[206] (evidence level 2+). Results were grouped according to type of event: first event, recurrent event or any event (distinction between first and recurrent events not possible). Lupus anticoagulants were found to be significantly associated with DVT. Five studies investigating lupus anticoagulants and anticardioplatin antibodies gave pooled odds ratios of 5.71 for any event and 9.4 for a first event. None of the studies showed a significant association with anticardioplatin antibodies. Four studies investigating lupus anticoagulants alone gave pooled odds ratios of 16.2 for any event and 4.01 for a recurrent event.

We identified one systematic review with 24 studies that looked at the association between raised homocysteine levels and venous thrombosis[156] (evidence level 2+). No information was given as to how venous thrombosis was diagnosed. The review showed that a 5µmol/L increase in measured plasma total homocysteine is associated with an increased risk of venous thrombosis (OR=1.27, 95% CI: 1.01 to 1.59 from three prospective studies, OR=1.60, 95% CI: 1.10 to 2.34 from 24 retrospective studies). The same review also looked at the association of MTHFR (Methylenetetrahydrofolate

reductase) with venous thrombosis. The 677TT genotype was associated with a 20% higher risk of venous thrombosis compared to the 677CC genotype (OR=1.20, 95% CI: 1.08 to 1.32).

We identified one systematic review that looked at the association between prothrombin gene mutation and venous thromboembolism[580] (evidence level 2+). In one study G20210a prothrombin was associated with a three fold increase in risk of venous thromboembolism (OR=2.8, 95% CI: 1.4 to 5.6). Similar results were found in a pooled analysis of eight case-control studies (OR=3.8, 95% CI: 3.0 to 4.9).

Rocha et al.[556] reported eight studies investigating the links between VTE and pro-thrombin gene mutation (evidence level 2+). These concluded that there was an increase in VTE with the mutation with odds ratios reported between 2.0 and 11.5.

Samama et al also looked at the association between elevated plasma levels of coagulation factors and venous thromboembolism[580]. Elevated factor VII, VIII, IX and XI were all found to be significantly associated with venous thromboembolism while elevated factor X or high plasma levels of fibrinogen were not.

Two externally produced guidelines, not specifically in surgical patients, considered risk factors for venous thromboembolism [219,591] and highlighted the following thormbophilic conditions that increased the risk of VTE: myeloprofilerative disease; paraproteinaemia; paroxysmal nocturnal haemoglobinuria and Behcet's Disease. Although these conditions were specifically mentioned within the risk factor list within the NICE guideline for reducing the risk of VTE in surgical in-patients[473], for simplicity it is intended that these conditions are included within the 'known thrombophilia' risk factor in the current guideline.

5.7.5 Varicose veins

Edmonds et al.[169] identified seven studies investigating the association between varicose veins and postoperative DVT (evidence level 2+). A pooled estimate of the six studies with data showed an increase risk (OR 2.39, 95% CI: 1.69 to 3.37). One study did not provide any data (Evidence Table 7, Appendix D).

Rocha et al.[556] investigated varicose veins, venous insufficiency and peripheral arterial disease as risk factors for VTE. Eight studies were found (evidence level 2+). Four studies reported significant increases in risk of VTE in medical patients with varicose veins (OR $\geq$ 2.5) although an additional two studies did not find an association. One study reported that the risk of VTE associated with varicose veins decreases with age. There was an increase in VTE risk found associated with venous insufficiency (OR $\geq$ 1.7) and peripheral arterial disease (OR = 1.9) (Evidence Table 7, Appendix D).

5.7.6 Cardiovascular factors

Edmonds et al[169] identified two studies looking at the association between cardiovascular factors and postoperative DVT (evidence level 2+). Three potential risk factors were identified: recent myocardial infarction, hypertension and congestive cardiac failure. None were shown to be significantly associated with postoperative DVT. Congestive cardiac failure was shown to be significantly associated with DVT in univariate analysis but not in multivariate analysis in two studies, suggesting that the association was potentially explicable by confounding. Another non-surgical study reported by Edmonds showed similar results (Evidence Table 8, Appendix D).

The systematic review by Rocha et al. [556] looked at two cardiovascular factors as risk factors for VTE, acute myocardial infarction and congestive heart failure (CHF) (evidence level 2+). The two studies included for the section on acute myocardial infarction were both RCTs and reported on the populations that did not receive prophylaxis, where they found a high incidence of DVT and PE (62.5% and 12.2% respectively). Five studies were found investigating CHF for VTE. They all reported an increase in VTE in medical patients who had CHF, with the risk increasing with decreasing ejection fraction and increasing functional compromise (Evidence Table 8, Appendix D)

5.7.7 Oral contraceptives

Edmonds et al[169] identified five cohort studies and two case control studies in surgical patients (evidence level 2+). A pooled risk estimate was only possible for three of the studies due to deficiencies in reported data. This showed oral contraceptive pills were significantly associated with an increased risk of postoperative DVT (OR=2.48, 95% CI: 1.53 to 4.02). Edmonds et al. reported some weaknesses with the data available: the studies were somewhat dated and may not apply to the recent third generation of oral contraceptive pills; and only three out of the five cohort studies screened everyone for DVT. Another systematic review compared third generation with second generation users in non-surgical populations[336] (evidence level 2+). Third generation contraceptives were associated with an increased risk of venous thrombosis compared to second generation contraceptives (unadjusted OR=1.6, 95% CI: 1.3 to 1.9; adjusted odds ratio OR=1.7, 95% CI: 1.4 to 2.0) (Evidence Table 9, Appendix D).

The Royal College of Obstetricians and Gynaecologists offers guidance on venous thromboembolism and hormonal contraceptives[564]. In addition, The BNF [313] states that:

> *"oestrogen-containing contraceptives should preferably be discontinued (and alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilisation of a lower limb'* [313].

The BNF recommends that progestogen only methods need not be discontinued prior to surgery even when immobilisation is expected{BNF2008].

If the decision to stop oral contraceptives is taken it is important that women are provided with advice on the use on contraceptives in the interim period. Further information is contained within the BNF.

5.7.8 Hormone replacement therapy

Edmonds et al{EDMONDS2004} found no studies investigating hormone replacement therapy in a surgical population. We identified two recent systematic reviews that identified studies from a non-surgical population. The Royal College of Obstetricians and Gynaecologists[562] identified nine studies but did not pool the relative risks, these varied from 2.1 to 6.9 (evidence level 2+). Miller et al[444] calculated a pooled relative risk of 2.14 (credible interval 1.64 to 2.81) from 12 studies (evidence level 2+). Six of these studies also compared the risk of hormone replacement use in the first year compared to subsequent years of use. Use in the first year had a higher risk estimate (relative risk in first year of use: 3.49, credible intervals: 2.33 to 5.59; relative risk in subsequent years of use: 1.91, credible intervals: 1.18 to 3.52) (Evidence Table 10, Appendix D).

Rocha et al.[556] identified two additional studies (evidence level 2+) published since the publication of Miller et al[444]. One was the Women's Health Initiative RCT which supported a higher rate of VTE in the group receiving HRT compared to the placebo

group (relative risk = 2.1; 95% CI = 1.6-2.8). The second study was a case control study which reported a higher VTE rate with oral hormone replacement therapy compared with transdermic administration (odds ratio: 4.0; 95% CI 1.9-8.3) (Evidence Table 10, Appendix D).

The Royal College of Obstetricians and Gynaecologists offers guidance on hormonal replacement therapy and venous thromboembolism[562]. In addition, the BNF also provides guidance indicating that HRT should be considered a risk factor for VTE but it may be prudent to consider stopping treatment 4-6 weeks before major surgery under general anaesthesia[313].Both BNF and RCOG documents highlights that stopping this may not necessary to stop prior to surgery provided that appropriate thromboprophylaxis is used.

5.7.9 Cancer

Edmonds et al[169] identified nine studies investigating the association between cancer and postoperative DVT (evidence level 2+). An assumption in the review is that an effect of cancer on thrombosis following general surgery is the same as the effect when surgery is for the treatment of that cancer. All nine studies found an increased risk associated with cancer giving a pooled odds ratio of 2.94 (95% CI: 2.01 to 4.29). Around a third of the total number of patients also received thromboprophylaxis (Evidence Table 11, Appendix D).

Rocha et al[556] identified 5 studies investigating the risk of VTE with various cancers (evidence level 2+). These studies indicated that although some cancers were associated with an increased risk of VTE (e.g. leukaemia, brain and uterus), others cancers had a lower relative risk of VTE compared to patients with no cancer (e.g. head and neck, bladder cancer, breast cancer). However, very little details are provided about these studies and the additional risk factors that the patient may have (e.g. surgery). A full list of the risk associated with 18 cancer types is presented in the evidence table (Evidence Table 11, Appendix D).

5.7.10 Chemotherapy

No surgical studies were found investigating the association between chemotherapy and postoperative DVT. We identified one systematic review of 32 studies that investigated vascular and neoplastic events associated with tamoxifen in non-surgical patient groups [79] (evidence level 1+). Eleven of the included studies reported pulmonary embolisms and demonstrated overall a significantly increased risk of pulmonary embolism (RR=1.88, 95% CI: 1.17 to 3.01) and 15 of the included studies reported DVT also demonstrating an increased risk (RR=1.87, 95% CI: 1.33 to 2.64). Seven of the 11 pulmonary embolism studies and 11 of the 15 DVT studies investigated the use of tamoxifen in patients with malignancy. The other four studies were for the prevention of cancer (Evidence Table 12, Appendix D).

Rocha et al.[556] reported an additional 5 studies (evidence level 2+). These studies reported significant increases in VTE when patients were 'on chemotherapy' compared with 'off chemotherapy' in breast cancer patients. In addition tamoxifen was highlighted as an additional factor increasing VTE risk for breast cancer patients in three studies. The use of thalidomide was observed to increase DVT in patients with multiple myeloma in another study (Evidence Table 12, Appendix D).

5.7.11 Smoking

Edmonds et al[169] identified four studies investigating the association between smoking and postoperative DVT (evidence level 2+). Two studies showed smokers to have significantly less DVTs than non-smokers; one study showed smoking to be protective in a univariate analysis but not in a multivariate analysis and the fourth study showed no difference. Overall, the studies suggest a non-significant association of fewer postoperative DVTs for smokers despite studies indicating it to be a risk factor for DVT in the general population. However, smoking is associated with other postoperative adverse events such as wound related or cardiopulmonary complications.

Rocha et al[556] did not find any evidence for smoking and venous thromboembolism.

5.7.12 Prolonged travel

Immobility associated with prolonged and continuous travel immediately before or after surgery may increase a patient's risk of developing postoperative VTE. We found no studies that specifically addressed this patient group. We identified one systematic review that investigated venous thromboembolism risk in long distance travel[24] (evidence level 2+). Long haul travel was shown to significantly increase risk (OR=1.59, 95% CI: 1.04 to 2.43) in three case control studies, (RR=2.93, 95% CI: 1.58 to 5.58 from two cohort studies). Two of the studies provided a risk estimate for any form of long distance travel, these also showed an increase risk of venous thrombosis (OR=2.6, 95% CI: 1.79 to 3.79). All the studies related to travel were in journeys over three hours. In three, travel related to the previous four weeks and in the fourth, travel related to the previous three weeks. Meaningful comparison between patients travelling for surgery and data from people on long haul flight is difficult. Long haul flight travellers are often healthier than the general population and, therefore, not a true sample[24] (Evidence Table 13, Appendix D).

Rocha et al[556] did not look for evidence on the any association between prolonged travel and venous thromboembolism.

5.7.13 Admission to critical care

Rocha et al[556], [556] identified admission to a critical care unit as an independent risk factor for VTE (Relative risk 1.8 to 2.9) (evidence level 2+). The review reports the incidence of DVT for patients within critical care as between 25-30% in the absence of prophylaxis. (Evidence Table 14, Appendix D)

5.7.14 Severe medical illness

The systematic review by Rocha et al [556] identified an increase in risk due to medical illnesses such as acute rheumatologic diseases and inflammatory bowel disease, infections, nephrotic syndrome, respiratory diseases and stroke (evidence level 2+) (Evidence Table 15-18, Appendix D). These acute medical illnesses were also identified in other guidelines as risk factors for VTE [219,591].

5.7.15 Reduced mobility

Rocha et al, 2007[556] identified three studies which investigated acute hemiplegia as a risk factor for VTE. One cohort study identified the incidence of VTE as 26% (no confidence intervals provided) and two case control studies identified paralysis as a significant risk factor for VTE compared with no paralysis (Evidence Table 19, Appendix D).The systematic review by Rocha et al[556] also reviewed the evidence for reduced

mobility (as opposed to paresis or paralysis of lower extremities) as a risk factor. Again, a significant association between VTE risk and mobility was identified, although the authors commented that the definition of mobility used in each of the studies was different which made it difficult to interpret these data (Evidence Table 21, Appendix D).

Within the recommendations in the guideline we have referred to 'significantly reduced mobility' as a risk factor. This was defined by the GDG as bed bound, unable to walk unaided or likely to spend a proportion of the day in bed or in a chair.

5.7.16 Duration of surgery

Both the work to determine the baseline risk of VTE (section 5.3) and the systematic review of risk in surgical patients[169] identified that VTE risk differed by surgery type. The GDG discussed this in conjunction with the evidence that reduced mobility increased the risk of VTE (section 5.7.15). They agreed that procedures involving general anaesthetic which would involve complete, prolonged immobilisation for the duration of the surgery would increase VTE risk. They agreed that patients undergoing surgery where the total anaesthetic time of 90 minutes should be considered for VTE prophylaxis. In addition, they noted that surgery of the pelvis and lower limbs had an increased risk of VTE (Table 5-17: Risk of DVT and pulmonary embolism by type of surgery, from the no prophylaxis arm of RCTsTable 5-17) and so for any operation in these regions an increased risk should be considered if the surgery time was 60 minutes or more.

5.7.17 Pregnancy and ≤6 weeks postpartum

Rocha et al[556] identified one retrospective case-reference study identifying the incidence of VTE in pregnant patients as 103:100,000 (95% CI: 55 – 177), which was higher than all women where the VTE incidence was 36:100,000 (95% CI: 29– 44) . The authors of the study noted that this incidence was higher than for those patients receiving combined oral contraceptives (Evidence Table 20, Appendix D).

The risk of VTE and prophylaxis for this population is discussed in more detail in chapter 30.

5.7.18 Discussion of data on patient risk

The identified systematic reviews of patient related risk factors varied in the quality of their evidence: the diagnosis of venous thromboembolism was not always achieved using an objective test (for example fibrinogen uptake test, ultrasound); only some of the studies provided the number of cases and controls on which the data were based; some studies gave pooled risk ratios for their results while others only provided the risk ratios for individual studies.

The evidence for risk factors is heterogenous in several ways:

- only some of our evidence comes from surgical populations and some from medcial patients,
- the way risk is measured differed between studies, some use odds ratios while others use relative risk,
- the amount and quality of the evidence differed considerably between risk factors.

We acknowledge that risk factor is information is difficult to use and the risk factors may be additive or interacting. Because of the uncertainty of how to use the risk factor evidence, and the different levels of risk within our included patients we have opted for a simplified approach to the recommendations. We have identified one list of risk factors that can be used in conjunction with accompanying recommendations for medical patients and surgical and trauma patients.

Some operations (e.g. elective hip replacement, elective knee replacement, surgery for fracture of the proximal femur) were felt to constitute a sufficiently high risk alone to warrant prophylaxis (chapters 10 to 12). For other surgery any patients with any of the risk factors in this list were felt to be at increased risk of VTE should be considered for prophylaxis.

5.8 Individual patient risk factors and relative risk of bleeding

Although many different studies have been completed on risk factors for VTE (section 5.7), he risk of bleeding in patients at risk of VTE does not appear to have studied as rigorously. A full search for bleeding risk factors in patients admitted to hospital was not completed.

During the process of developing recommendations for VTE prophylaxis the GDG identified that assessing the bleeding risk was key and that it needed to be considered prior to offering pharmacological prophylaxis in order to reduce the risk of harm.

The risk factors included in the risk factor list were identified from a number of different sources including exclusion criteria from the randomised controlled trials included in our systematic review, from cautions included in the summary of product characteristics for pharmacological VTE prophylactic agents and the clinical expertise of the GDG. As such, no quantitative assessment of the relative risk of bleeding for each of the factors included in the list was possible.

5.9 Recommendations and link to evidence

The Guideline Development Group felt that while the available quantitative information on relating to absolute risk of VTE and major bleeding had important shortcomings, it was important to collate and report these data. The Guideline Development Group opted to utilise the available data in a semi-quantitative manner as outlined in the following recommendations.

Recommendation	**Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).**
Trade off between clinical benefit and harms	The risks of VTE must be identified to determine whether the patients are at increased risk of the condition in order for a decision about whether prophylactic measures are appropriate. In order for this decision to be made the risk of VTE must be assessed.
Economic considerations	No cost-effectiveness model was completed to answer whether risk assessment was cost effective. There will be some cost associated with the resources required to complete the risk assessment. However, the benefits of identifying patients at an increased risk of VTE were felt to outweigh the costs of administering the risk assessment tool.

Other considerations	The Guideline Development Group agreed that the best way to ensure that all patients were risk assessed for VTE was to complete the assessment at the initial admission to hospital. This should allow the high risk patients to be identified early and should allow appropriate prophylaxis to be administered without delay.
Recommendation	**Regard medical patients as being at increased risk of VTE if they:** • **have had or are expected to have significantly reduced mobility for 3 days or more, or** • **are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.**
Box 1 – Risk factors for VTE	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a family history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The main venous thromboembolic outcomes when considering risk factors were asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism.
Trade off between clinical benefit and harms	The decision of whether to provide prophylaxis will be a balance between the increased risk of VTE for the individual patient balanced against their risk of bleeding. The only way that this balance can be determined is by identifying which risk factors for VTE that each patient has.
Economic considerations	No cost-effectiveness model was completed to answer whether risk assessment was cost effective. However, the benefits of identifying patients at an increased risk of VTE were felt to outweigh the costs of administering the risk assessment tool.

Many of the individual risk factors that were identified as establishing a person as 'increased risk' for VTE (e.g. reduced mobility with severe medical illness, critical care admission) were criteria for inclusion in the randomised trials on which the cost effectiveness of treatments were based (Chapter 23). Other factors were patients were groups who were generally excluded from the trial evidence (e.g. known thrombophilias) but are likely to have a risk of VTE at least as high as those patients included in the trials and are discussed in section 5.7.

Quality of evidence

All of the risk factors in the list in the recommendation and in box 1 were established from the evidence from systematic reviews on individual patient risk factors as presented in section 5.7 except for dehydration which is presented in section 7.3. The limitations of the evidence were that the risk factors within the systematic reviews were from many small studies which had different populations and for medical patients no attempts were made to statistically pool these data. No information about the interaction or additive effect of risk factors was identified within the literature.

Other considerations

During the consultation period a stakeholder commented that 'ongoing reduced mobility relative to their normal state' may be a term which required further explanation. The GDG discussed this term at length and felt that this should include any time at home with reduce mobility. They concluded that it was not possible to include precise time for this reduced mobility and that this factor would need clinical judgement according to the individual affected.

Recommendation	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more risk factors shown in Box 1.**

Box 1 – Risk factors for VTE	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a family history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The main venous thromboembolic outcomes considered were asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism.
Trade off between clinical benefit and harms	The decision of whether to provide prophylaxis will be a balance between the increased VTE risk for the individual patient balanced against their risk of bleeding. The only way that this balance can be determined is by identifying which factors the patient has which increase the risk of VTE.
Economic considerations	No cost-effectiveness model was completed to answer whether risk assessment was cost effective. However, the benefits of identifying patients at an increased risk of VTE were felt to outweigh the costs of administering the risk assessment tool. Many of the individual risk factors that were identified as establishing a person as 'increased risk' for VTE.
Quality of evidence	All of the risk factors in the recommendation and in box 1 were established from the evidence from systematic reviews on individual patient risk factors as presented in chapter 5.7 except for dehydration which is detailed in section 7.3. The limitations of the evidence were that the risk factors within the systematic reviews were from many small studies which had different populations and which were sometimes difficult to draw accurate conclusions from. No information about the interaction or additive effect of risk factors was identified within the literature.
Other considerations	The risk factor list is different to that presented in the previous surgical guideline[473]. The changes were made in order to clarify and simplify the list of risk factors and to allow one list for all patients admitted to hospital which aims to improve the ease of use in hospital. Five of the risk factors in the previous guideline (active heart or respiratory failure, acute medical

illness, nephrotic syndrome, recent myocardial infarction or stroke and severe infection) were included under the heading 'one or more significant medical comorbidity'

Five of the more specific conditions listed as risk factors in the surgical guideline (antiphospholipid syndrome, behcet's disease, myeloproliferative diseases, paraproteinaemia and paroxysmal nocturnal haemoglobinuria) are included within the 'known thrombophilias' risk factor in this guideline. This decision was taken in order to make the list simpler to use in practice. The GDG felt that junior doctors who might be completing the risk assessment should have an understanding on the conditions constituting 'known thrombophilias'.

Continuous travel was removed from the list as it was felt that the evidence for this was not strong and the risk factor was really immobility rather than travel and hence captured elsewhere.

The inclusion criteria for the previous surgical guideline[473] were all patients undergoing surgery with an overnight stay. As the current guideline extends the inclusion criterion to all patients admitted to hospital the timing of surgical procedure was felt to be a helpful guideline to identy people at risk.

Recommendation	**Reassess patients' risk of bleeding and VTE within 24 hours of admission, and whenever the clinical situation changes, to:** • **ensure that the methods of VTE prophylaxis used are suitable** • **ensure that VTE prophylaxis is being used correctly** • **identify adverse events resulting from VTE prophylaxis.**
Trade off between clinical benefit and harms	The complete picture of the VTE risk for the individual patient may not be entirely clear when first assessed upon admission. In order to ensure that patients are treated appropriately, the Guideline Development Group felt it was important that the patient is reassessed.
Economic considerations	No cost-effectiveness model was completed to answer whether reassessment of risk was cost effective. There will be a cost associated with the resources required to complete the reassessment of VTE risk. However, the benefits of identifying patients at an increased risk of VTE (or of identifying those whose risk is lower than had been previously assessed) were felt to outweigh the cost of completing the assessment. It is clear that the cost-effectiveness of prophylaxis is dependent on maintaining adherence and preventing complications. In our cost-effectiveness analyses comparing different types of prophylaxis (Chapter 4) we included the cost

of clinician time for the administration of prophylaxis.

Other considerations

All of the Guideline Development Group agreed that reassessment of VTE was important, however the timing of the second assessment was more controversial that the first assessment on admission to hospital. There is no evidence for reassessing VTE risk 24 hours after the first assessment, but the Guideline Development Group felt that at this time diagnostic tests required for each patient would have been completed and the bleeding risks were likely to be better established. Some Guideline Development Group members were concerned about the resources available for this recommendation but felt that by providing a timeframe it was more likely to occur.

In addition the Guideline Development Group felt that when the clinical situation changed there was need to reassess the VTE risk of patients to ensure the appropriate prophylaxis is established or continued.

Recommendation	**Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.** ***The summary of product characteristics for the pharmacological thromboprophylaxis being used or planned should be consulted for further details.***
Box 2. Risk assessment - Bleeding	**Regard hospitalised patients as being at risk of bleeding if they have any of the following risk factors:** • **Active bleeding** • **Acquired bleeding disorders (such as acute liver failure)** • **Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)** • **Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours** • **Lumbar puncture/epidural/spinal analgesia within the previous 4 hours** • **Acute stroke** • **Thrombocytopenia (platelets less than 75 x 10^9/l)** • **Uncontrolled systolic hypertension (230/120 mmHg or higher)** • **Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease).**
Trade off between clinical benefit and harms	For each of the recommendations about providing prophylaxis the potential benefits of reducing the risk of VTE events (symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism) needs to be balanced against the potential harms of bleeding events (major bleeding, fatal bleeding and stroke). In some patients the risk of bleeding is not cost effective.
Economic considerations	Where cost effectiveness models have been developed and run for different sub-populations within the guideline (Chapters 9-12, 23) the bleeding risk used has been the average bleeding risk of patients within the individual trials. It is known that most of the trials will have excluded patients with a high risk of bleeding and so the recommendations as made in the chapters may not be appropriate to the high bleeding risk population.
Other considerations	The Guideline Development Group developed a list of clinical indications where the risks of bleeding should be carefully considered before providing pharmacological prophylaxis. This list of factors in box 2 was based on the exclusion criteria used in the trials of pharmacological VTE agents in our systematic review, information from the summary of product

	characteristics and the experience of the clinicians within the guideline development group. The list was then modified based on stakeholder comments during consultation. No quantitative assessment of the relative risk of bleeding for each of the factors included in the list was possible. The GDG felt it was important to reference to the summary of product characteristics as the timing of provision of pharmacological VTE may differ according to the half life of the different agents being used, or planned and needs to be within licensed indication. For example, fondaparinux has a half life of 17-21 hours which is longer than low molecular weight heparins.
Recommendation	**Advise patients to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods.**
Relative values of different outcomes	The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The increased risk of VTE through use of oestrogen containing oral contraceptives and hormone replacement therapy was considered.
Economic considerations	No cost effectiveness model was completed to identify the cost effectiveness of stopping these treatments before surgery. The guideline development group felt that the benefits in terms of reducing the risk of VTE after surgery may, in some patients, outweigh the benefits of maintaining therapy, and so felt that it should be considered for all relevant patients.
Quality of evidence	The systematic reviews of risk factors for VTE identified oestrogen containing oral contraceptives and hormone replacement therapy as factors which significantly increased the risk of VTE (section 5.7.7 and 5.7.8). These treatments although improve the quality of the patient's life are unlikely to be life threatening if stopped. Therefore consideration should be given to their continued use.
Other considerations	This recommendation is based on the recommendation from the previous surgical guideline. The Guideline Development Group used both the evidence from systematic reviews and advice provided in the BNF[313], which included the advice of when to stop these hormone treatments before elective surgery (4-6 weeks). Additional guidance can be found in the RCOG guidelines on guidance on venous thromboembolism and hormonal contraceptives[564] and hormonal replacement therapy and

venous thromboembolism [562], and the BNF[313] .

One issue raised by several stakeholders during consultation was the need to provide intervening contraceptive advice where the decision is made to stop oral contraceptives. A sentence has now been added to the recommendation to specify this.

Recommendation	**Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery. Consider involving the multidisciplinary team in the assessment.**
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. The group of patients who are receiving antiplatelet or anticoagulation therapy before surgery are at an increased risk of bleeding.
Economic considerations	No cost effectiveness model was completed to identify the cost effectiveness of stopping these treatments before surgery. The guideline development group felt that the benefits in terms of reducing the risk of bleeding after surgery may, in some patients, outweigh the benefits of maintaining therapy, and therefore felt that it should be considered for all relevant patients.
Other considerations	This recommendation is based on the recommendation from the previous surgical guideline. This recommendation needs to be carefully considered in the context of the individual patient and should take into consideration all of their existing or potential comorbidities that may occur from stopping treatment. In order to balance these factors, advice from different disciplines may be needed. The BNF should be consulted for appropriate timing for stopping and restarting antiplatelet therapies around surgery. Current advice suggests that antiplatelets should be stopped 1 week before surgery.

5.10 Recommendations for research

5.10.1 Research question 1

- What is the absolute risk of VTE among different groups of hospital patients and can the risk be reliably estimated on admission to hospital to ensure that appropriate patients are offered VTE prophylaxis?

Why this is important

One of the most difficult areas the Guideline Development Group faced when developing the guideline was to identify the absolute risk of VTE among specific patient groups in relation to the reason for admission. A new, large pragmatic cohort study and/or record linkage study using Hospital Episode Statistics and the General Practice Research Database is proposed. This would allow all people admitted to hospital to be studied to identify those who develop VTE, including people who are diagnosed with VTE in primary care after discharge from hospital. Information on baseline patient-related factors, procedures and duration of stay, complications, prophylactic therapies and concomitant drug use should be collected and analysed. It should allow the identification of independent risk factors for VTE and the development and subsequent validation of a risk model to estimate the absolute risk of VTE in individual patients. This research would allow clearer identification of those patients at risk of VTE and those in whom the risk is so low that the bleeding risk of pharmacological VTE prophylaxis would add overall hazard.

Recommended study design: Cohort/ record linkage study.

5.10.2 Research question 2

- What is the incidence, loss of quality of life and cost associated with post-thrombotic syndrome after potentially preventable deep vein thrombosis?

Why this is important

During development of the guideline it became apparent that the incidence of post-thrombotic syndrome, particularly after asymptomatic deep vein thrombosis, was not well reported. This study should use standard, validated definitions to identify the incidence of post-thrombotic syndrome both when a deep vein thrombosis has occurred as a result of a hospital admission and in the absence of hospital-acquired deep vein thrombosis. The study also should aim to identify the costs to the NHS of treating post-thrombotic syndrome.

Recommended study design: Cohort

5.11 Summary of recommendations

- Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).

- Regard medical patients as being at increased risk of VTE if they:
    - have had or are expected to have significantly reduced mobility for 3 days or more **or**

    - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

- Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
    - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb

- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors shown in Box 1.

Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a family history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

- Reassess patients' risk of bleeding and VTE within 24 hours of admission, regularly thereafter and whenever the clinical situation changes, to:
  - ensure that the methods of VTE prophylaxis used are suitable
  - ensure that VTE prophylaxis is being used correctly
  - identify adverse events resulting from VTE prophylaxis.
- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.

* The summary of product characteristics for the pharmacological thromboprophylaxis being used or planned should be consulted for further details.

Box 2. Risk factors for bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

- Advise patients to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods.

- Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery. Consider involving the multidisciplinary team in the assessment.

12 Hip fracture surgery

12.1 Introduction

Fractures of the proximal femur (commonly known as neck of femur or hip fractures) are very common in the elderly population and carry significant morbidity and mortality. They occur mainly as osteoporotic or fragility fractures but a small proportion may result from major trauma in a younger age group. The latter is covered under the section on major trauma (Section 22).

We have estimated from the incidence of RCTs that the risk of developing DVT, pulmonary embolism and major bleeding in patients with fractures of the proximal femur not receiving thromboprophylaxis is:

- DVT (symptomatic and asymptomatic) - 37% (95% CI: 35% to 40%)
- Symptomatic pulmonary embolism – 6% (95% CI: 4% to 7%)
- Major bleeding events – 2% (95% CI: 1% to 3%)

It is likely from the evidence available that the incidence of each is greater in this patient group with an additional impact mainly from cardiovascular, respiratory and cerebrovascular disease. Therefore, the risks of adding mechanical and pharmacological VTE prophylaxis have to be weighed very carefully against any potential adverse effects of this treatment. However, there is some evidence from the studies evaluated for this guideline that there is a reduction in VTE events if thromboprophylaxis is used. This effect is greater in proportion than the risk of adverse events, in particular, major bleeding.

12.2 Evidence of methods of prophylaxis

12.2.1 Summary of comparisons identified for any outcome

Thirty randomised controlled trials which reported at least one of the three main outcomes were identified[51,74,172,175-178,185,204,209,248,316,370,381,458,463-465,470,533,541,590,609,613,621,630,631,700,704,715]. Some of these investigated more than two methods of thromboprophylaxis. Most of RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Six systematic reviews included RCTs covering patients with hip fracture[21,125,355,451,557,719].

Another two studies investigated thromboprophylaxis in a mixed population of both hip fracture and elective hip replacement patients[122,459].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm
GCS													
IPCD/FID	**1**												
Dabigitran													
Fondaparinux		**1**											
LMWH	**2**					**1**							
UFH	**7**						**2**						
VKA	**6**												
High dose aspirin	**7**							**3**	**1**				
Low dose aspirin													
GCS + IPCD/FID				**1**									
Mech + pharm								**1**					
Other comparisons							**1**				**1**		

Figure 12-31: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

12.2.2 Results from pairwise comparisons

Table 12-71: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
IPCD/FID vs nil[185]	1	4/145	9/159	0.49 (0.15, 1.55)	-0.03 (-0.07, 0.02)	ET: 24 FP: 4
LMWH vs nil[316,613]	2	33/102	78/116	0.48 (035, 0.65)	-0.35 (-0.48, -0.23)	ET: 26 FP: 13
UFH vs nil[51,209,370,464,631,704]	6	63/236	115/228	0.56 (0.39, 0.81) (a)	-0.23 (-0.35, -0.12)	ET: 27 FP: 17
VKA vs nil[74,248,463,470,533]	5	57/245	132/240	0.44 (0.34, 0.56)	-0.32 (-0.40, -0.24)	ET: 28 FP: 21
High dose asp vs nil[172,464,533,590,609,700,715]	7	117/385	116/338	0.85 (0.62, 1.15) (b)	-0.15 (-0.05, 0.05)	ET: 29 FP: 28
Single proph vs single						
Fon vs LMWH[175]	1	49/624	117/623	0.42 (0.31, 0.57)	-0.11 (-0.15, -0.07)	ET: 31 FP: 44
LMWH vs UFH[381,458]	1	14/53	23/54	0.62 (0.36, 1.07)	-0.16 (-0.34, 0.02)	ET: 32 FP: 48
VKA vs high dose asp[533]	1	13/65	27/66	0.49 (0.28, 0.86)	-0.21 (-0.36, -0.06)	ET: 35 FP: 60
Double proph vs single						
UFH + GCS vs GCS[465]	1	10/29	8/23	0.99 (0.47, 2.10)	0.00 (-0.26, 0.26)	ET: 27 FP: 142
Other prophylaxis strategies						
IPCD then LMWH vs LMWH[177]	1	2/21	4/24	0.57 (0.12, 2.81)	-0.07 (-0.27, 0.12)	ET: 51 FP: 209
Post discharge						
Fondaparinux[176]	1	3/208	74/218	0.04 (0.01, 0.13)	-0.33 (-0.39, -0.26)	ET: 57 FP: 221

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*
Proph - prophylaxis
(a) Significant statistical heterogeneity within the results (I^2 = 54%, p=0.03)
(b) Significant statistical heterogeneity within the results (I^2 = 60.3%, p=0.02)

Table 12-72: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
IPCD/FID vs nil[185] (a)	1	6/145	9/159	0.73 (0.27, 2.00)	-0.02 (-0.06, 0.03)	ET: 24 FP: 5
UFH vs nil[204,464]	2	1/74	2/74	0.50 (0.05, 5.34)	-0.01 (-0.06, 0.04)	ET: 27 FP: 18
VKA vs nil[74,178,463,470,533]	5	4/307	28/303	0.21 (0.08, 0.53)	-0.07 (-0.11, -0.03)	ET: 28 FP: 22
High dose asp vs nil[172,464,533,590,609,700,715]	7	12/385	26/338	0.44 (0.22, 0.88)	-0.03 (-0.06, -0.01)	ET: 29 FP: 29
Single proph vs single						
Fon vs LMWH[175]	1	3/831	3/840	1.01 (0.20, 4.99)	0.01 (-0.01, 0.01)	ET: 31 FP: 45

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
LMWH vs UFH[458]	1	6/46	0/42	11.89 (0.69, 204.91)	0.13 (0.03, 0.23)	ET: 32 FP: 49
VKA vs high dose asp[533]	1	0/65	1/66	0.34 (0.01, 8.16)	-0.02 (-0.06, 0.03)	ET: 35 FP: 61
Double proph vs single						
UFH + GCS vs GCS[465]	1	2/29	1/23	1.59 (0.15, 16.42)	0.03 (-0.10, 0.15)	ET: 27 FP: 143
Aspirin + other prophylaxis vs other prophylaxis (b)[541]	1	46 /6679	81 /6677	0.57 (0.40, 0.81)	-0.01 (-0.01, 0.00)	ET: 42 FP: 165
Other prophylaxis strategies						
IPCD then LMWH vs LMWH[177]	1	1/21	0/24	3.41 (0.15, 79.47)	0.05 (-0.07, 0.17)	ET: 51 FP: 210
Extended duration						
Fondaparinux[176]	1	0/326	3/330	0.14 (0.01, 2.79)	-0.01 (-0.02, 0.00)	ET: 57 FP: 222

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*
Proph - prophylaxis
(a) Asymptomatic and symptomatic pulmonary embolism

Table 12-73: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[316]	1	0/41	0/41	not estimable	0.00 (-0.05, 0.05)	ET: 26 FP: 15
UFH vs nil[51,204,464,704]	4	4/129	6/123	0.69 (0.23, 2.13)	-0.01 (-0.05, 0.03)	ET: 27 FP: 19
VKA vs nil[74,178,248,463,533]	5	26/312	18/310	1.35 (0.70, 2.62)	0.02 (-0.03, 0.06)	ET: 28 FP: 23
High dose asp vs nil[172,464,533,590,609,700,715]	87	8/385	10/338	0.52 (0.14, 1.96) (b)	-0.01 (-0.03, 0.01)	ET: 29 FP: 30
Single proph vs single						
Fon vs LMWH[175]	1	18/831	19/842	0.96 (0.51, 1.82)	0.00 (-0.02, 0.01)	ET: 31 FP: 46
VKA vs high dose asp[533]	1	5/65	1/66	5.08 (0.61, 42.28)	0.06 (-0.01, 0.13)	ET: 35 FP: 62
Double proph vs single						
UFH + GCS vs GCS[465]	1	0/29	0/23	not estimable	0.00 (-0.07, 0.07)	ET: 27 FP: 144
Other prophylaxis strategies	-	-	-	-	-	
Post discharge						
Fondaparinux[176]	1	8/327	2/329	4.02 (0.86, 18.81)	0.02 (0.00, 0.04)	ET: 57 FP: 223

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*
Proph - prophylaxis

12.2.3 Additional information

12.2.3.1 All cause mortality

Table 12-74: Mortality – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[316]	1	3/30	4/38	0.95 (0.23, 3.92)	-0.01 (-0.15, 0.14)	ET: 26 FP: 16
UFH vs nil[51,204,631]	3	20/193	20/187	0.96 (0.55, 1.67)	-0.01 (-0.08, 0.07)	ET: 27 FP: 20
VKA vs nil[74,178,248,463,470,533]	6	47/362	62/365	0.76 (0.54, 1.07)	-0.01 (-0.05, 0.03)	ET: 28 FP: 24
High dose asp vs nil[172,464,533,590,609,700,715]	7	23/385	25/338	0.75 (0.42, 1.34)	-0.01 (-0.04, 0.03)	ET: 29 FP: 31
Single proph vs single						
Fon vs LMWH[175]	1	38/831	42/842	0.92 (0.60, 1.41)	-0.00 (-0.02, 0.02)	ET: 31 FP: 47
LMWH vs UFH[381,458]	2	6/99	5/98	1.17 (0.35, 3.90)	0.01 (-0.05, 0.07)	ET: 32 FP: 51
VKA vs high dose asp[533]	1	2/65	3/66	0.68 (0.12, 3.92)	-0.01 (-0.08, 0.05)	ET: 35 FP: 63
Double proph vs single						
UFH + GCS vs GCS[465]	1	0/29	3/23	0.11 (0.01, 2.11)	-0.13 (-0.28, 0.02)	ET: 27 FP: 145
Post discharge						
Fondaparinux[176]	1	6/327	8/329	0.75 (0.26, 2.15)	-0.01 (-0.03, 0.02)	ET: 57 FP: 224

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*
Proph - prophylaxis

12.2.3.2 Additional outcomes

No RCTs or systematic reviews reported results for post thrombotic syndrome, chronic thromboembolic pulmonary hypertension, heparin induced thrombocytopenia, quality of life or length of stay as outcomes for this population.

12.2.3.3 Additional studies

Two RCTs investigated thromboprophylaxis in a mixed group of hip fracture and elective hip replacement patients. These have not been included in the above section and were not included in the economic model for either hip fracture or elective hip replacement:

- Cohen et al[122] found there was no significant difference in DVT or pulmonary embolism when stockings for 35 days were added to fondaparinux for five to nine days. (Appendix D, Evidence table 40; Appendix E, Forest plots 170-172)

- Monreal et al[459] found there was no significant difference in DVT or major bleeding when aspirin was added to UFH. (Appendix D, Evidence table 42; Appendix E, Forest plots 161, 163)

12.3 Network meta-analysis results

12.3.1 Introduction

A network meta-analysis was completed for DVT, major bleeding and all cause mortality. Details on the network meta-analysis methods can be found in section 3.10.

For patients undergoing surgery for fractures of the proximal femur the studies of standard duration prophylaxis (e.g. prophylaxis given for a maximum of 21 days) were analysed in the network meta-analysis. Prophylaxis extending beyond this period was analysed in a separate cost-effectiveness analysis.

12.3.2 Results

DVT results

There were 23 studies included in the network meta-analysis for DVT [51,74,172,175,177,185,209,248,316,370,381,463,464,470,533,590,609,613,631,700,704,715]. One study compared three interventions[533].

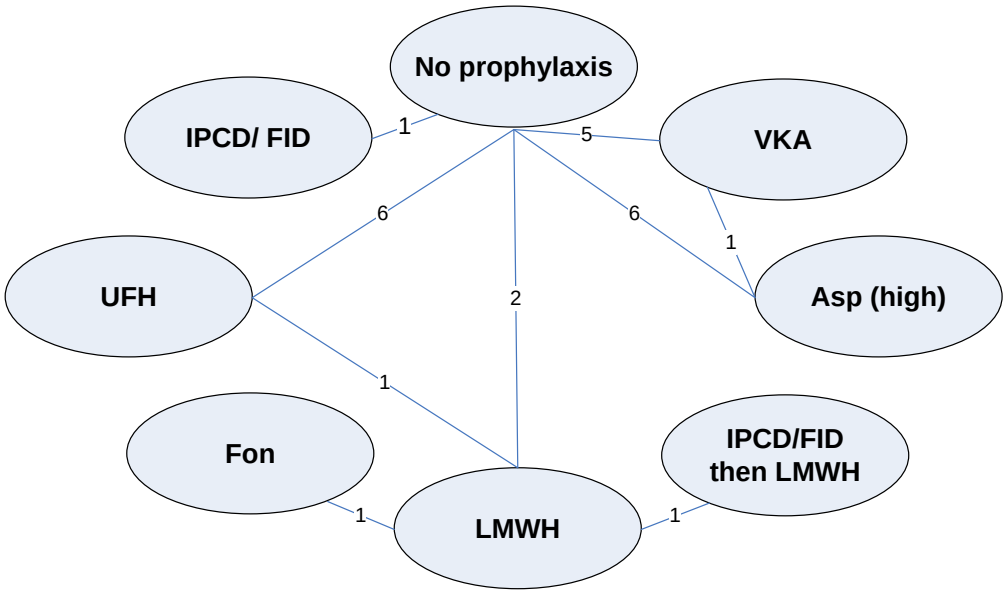

Figure 12-32: Network diagram for DVT. Numbers indicate the number of studies, which contributed results for each comparison

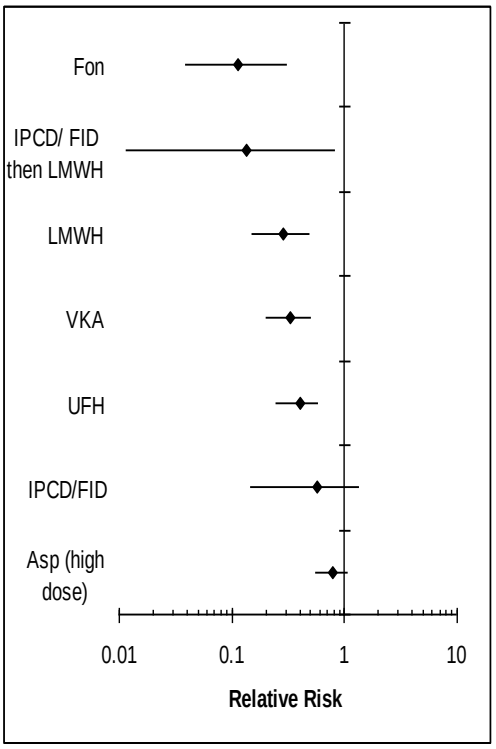

Figure 12-33: DVT – network meta-analysis results of interventions compared to no prophylaxis

Table 12-75: DVT – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Fondaparinux	0.11 (0.04, 0.31)
IPCD/FID then LMWH	0.14 (0.01, 0.82)
LMWH	0.29 (0.15, 0.50)
VKA (adjusted-dose)	0.33 (0.20, 0.51)
UFH	0.41 (0.25, 0.59)
IPCD / FID	0.58 (0.15, 1.37)
Asp (high dose)	0.79 (0.56, 1.07)

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 56.0, which is quite close to the number of data points of 47, implying that the model fits the data well.

Pulmonary embolism results

There were not enough data to complete a network analysis for this outcome

Major bleeding results

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in **medical patients**[45,121,191,256,257,350,387,390,394,579],
- 48 studies were in **general surgery patients**[10,14,29,40,50,52,72,75,76,92,113,199,210,227,230,238,262,266,267,269,280,283,321,324,329,358,366,385,439,496,499,503,504,516,517,530,552,553,570,575,588,589,633,639,641,645,657,667,703,711,713],
- 28 studies were in **elective hip replacement patients**[126,129,151,153,174,188,195,201,202,243,260,293,299,377,380,400,409,421,465,527,573,574,635,650,651,659,684],
- 9 studies were in patients undergoing **hip fracture surgery**[175,178,204,248,463,533,609,704,715]

- 15 studies were in **elective knee replacement patients**[36,66,130,186,201,202,274,388,389,399,436,476,479].
- 7 studies were in **mixed orthopaedic surgery patients**[69,200,242,250,292,459,531]
- 11 studies were in **mixed surgery patients**[54,166,270,271,340-344,396,416,486,568,569,575,585,655].

Seven of these studies included three comparison arms[153,299,380,504,533,633,655].

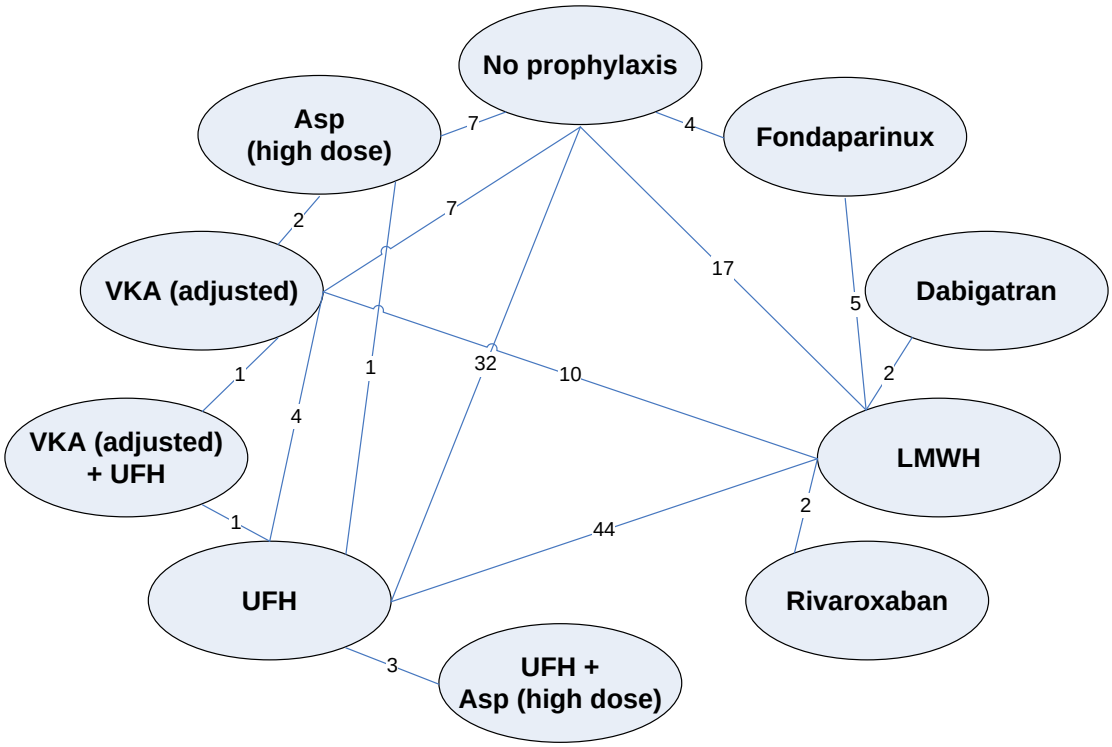

Figure 12-34: Network diagram for major bleeding. Numbers indicate the number of studies which contributed results for each comparison

Only the results for interventions included in the network meta-analysis for DVT were included in the results.

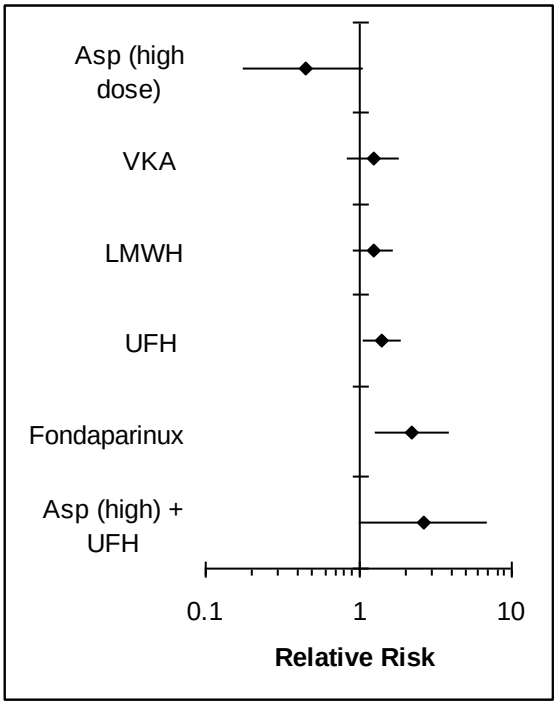

Figure 12-35: Major bleeding – network meta-analysis results of interventions compared to no prophylaxis

Table 12-76: Major bleeding – network meta-analysis results (pooled across all population subgroups)

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Asp (high dose)	0.45 (0.18, 1.07)
VKA	1.24 (0.83, 1.85)
LMWH	1.26 (0.94, 1.71)
UFH	1.43 (1.08, 1.92)
Fondaparinux	2.22 (1.30, 3.88)
Aspirin + UFH	2.69 (1.02, 6.91)

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 291.5, which is quite close to the number of data points of 263, implying that the model fits the data quite well.

All cause mortality

There were 18 studies included in the network meta-analysis for all cause mortality[51,74,172,175,178,204,248,316,380,458,463,470,533,590,609,631,700,715]. One study compared three interventions[533].

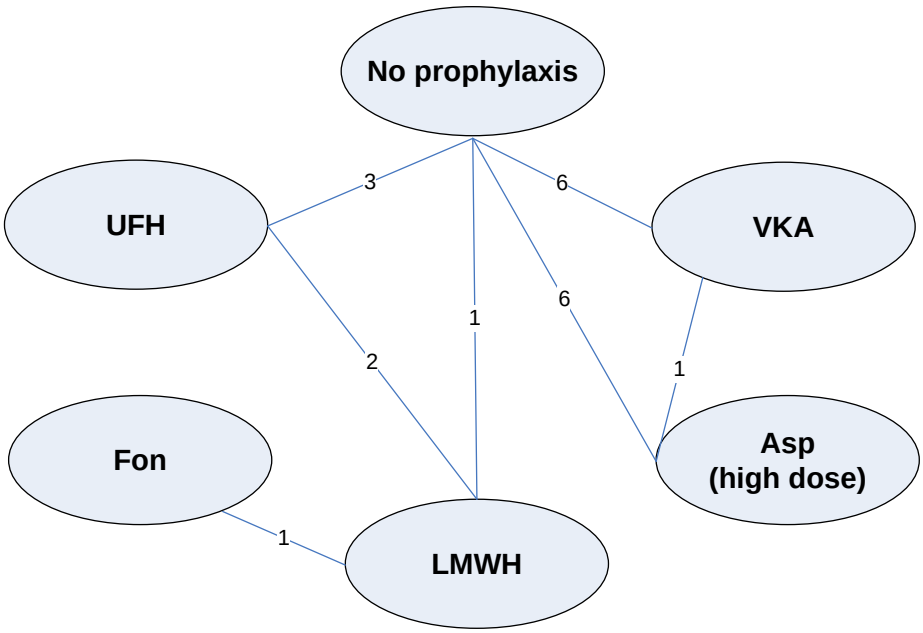

Figure 12-36: Network diagram for all cause mortality. Numbers indicate the number of studies which contributed results for each comparison

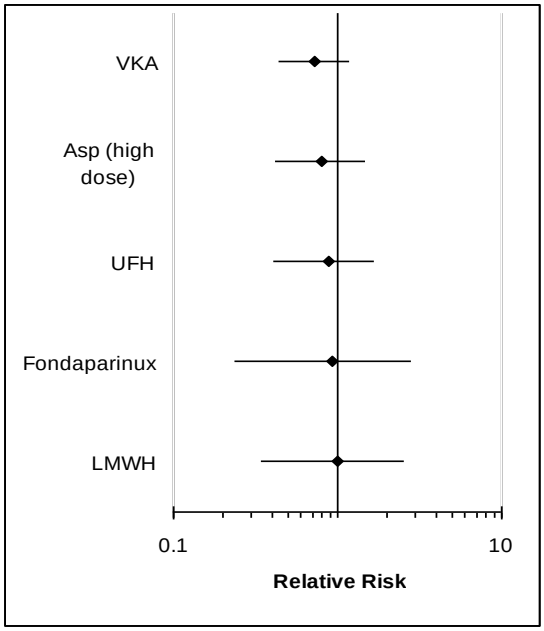

Figure 12-7: All cause mortality – network meta-analysis results of interventions compared to no prophylaxis

Table 12-77: All cause mortality – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
VKA	0.73 (0.44, 1.18)
Asp (high dose)	0.81 (0.42, 1.47)
UFH	0.88 (0.41, 1.68)
Fondaparinux	0.93 (0.24, 2.85)
LMWH	1.00 (0.35, 2.55)

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 33.5, which is quite close to the number of data points of 37, implying that the model fits the data well.

12.4 Cost-effectiveness evidence

12.4.1 Introduction

The general assumptions and methods for the cost-effectiveness model are described in chapter 4.

The results are driven by the network meta-analysis, above. Other data used for the cost-effectiveness analysis which are specific to hip fracture patients can be found in Table 12-76, Table 12-78 and Table 12-79.

Table 12-78: Baseline risk and other population specific parameters used in the economic model for hip fracture patients

Baseline Characteristics	*Source*	*Value*
Mean age (years)	Hospital Episode Statistics data 2005-6[159]	82
% Male	Hospital Episode Statistics data 2005-6[159]	23%
Standardised Mortality Ratio(a)	Seagroatt, 1994 [595]	461% (1 year)
Mean duration of prophylaxis	Systematic review of RCTs(b)	10 days
Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)	Assumed to be the same as elective hip replacement.	21.0%
Major Bleed Fatality Rate (c)	Muntz (2004) systematic review of thromboprophylaxis RCTs[467]	0.8% (5/632)
PE Fatality Rate (d)	Systematic review of RCTs (b)	31.0% (9/21)
DVT risk	Systematic review of RCTs (b)	39.8%
Symptomatic PE risk	Systematic review of RCTs (b)	7.9%
Major bleeding risk	Systematic review of RCTs (b)	3.2%

a) *Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex*
b) *This refers to the systematic review of RCTs for the current guideline*
c) *Fatal major bleeds divided by all major bleeds*
d) *Fatal PEs divided by all symptomatic PEs*

Table 12-79: Weights used for events in the base case analysis

Event	Cost (£)	QALYs lost	Net loss* (£)
DVT Asymptomatic	0	0.0000	0
DVT Symptomatic	576	0.0035	645
Post-thrombotic syndrome	3,427	0.0801	5,030
Chronic pulmonary hypertension	69,123	0.9672	88,467
Pulmonary embolism - fatal	0	4.3044	86,089
Pulmonary embolism - symptomatic	2,521	0.0041	2,603
Major bleeding - No long-term sequalae	908	0.0267	1,441
Major bleeding - Stroke	23,877	2.2410	68,696
Major bleeding - fatal	0	4.3044	86,089
Heparin-induced thrombocytopaenia (sensitivity analysis only)	2,428	0.6395	15,219

QALY=quality-adjusted life-year
** Net loss is the sum of the resource cost plus the QALY loss:*
Net loss=cost+ (20,000 x QALYs lost)

Event rates by strategy can be found in Appendix G.

12.4.2 Results: standard duration prophylaxis

12.4.2.1 Base case results

Table 12-80: Base case results – deterministic and probabilistic results

	Deterministic INB	*Probabilistic INB*	
Intervention (ordered by mean probabilistic INB)	*Mean*	*Mean*	*% of simulations where strategy was most cost-effective*
Fondaparinux	2151	2148	85.0%
WarfarinAD	1835	1830	4.2%
LMWH	1713	1711	4.5%
UFH	1470	1465	0.6%
IPCD-FID	979	999	5.7%
AspirinHD	560	558	0.0%
Nil	0	0	0.0%

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost-effective overall

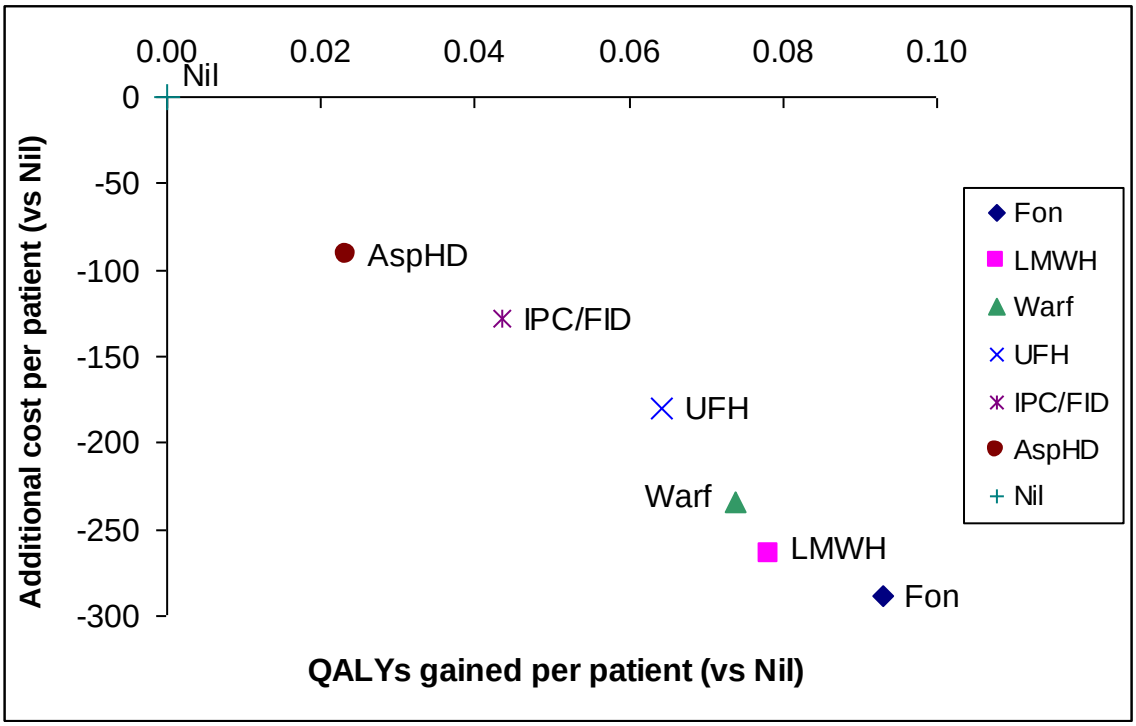

Figure 12-7: Base case results of the cost-effectiveness analysis for hip fracture patients: standard duration prophylaxis

Fon = fondaparinux, Warf = warfarin, QALY=quality-adjusted life-year

12.4.3 Base case results – post discharge prophylaxis

Table 12-81: Results for study post discharge comparing LMWH with no prophylaxis

	Deterministic INB	*Probabilistic INB*	
Intervention (ordered by mean probabilistic INB)	**Mean**	**Mean**	**% of simulations where strategy was most cost-effective**
Fondaparinux	262	239	92.0%
Nil	0	0	8.0%

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost-effective overall

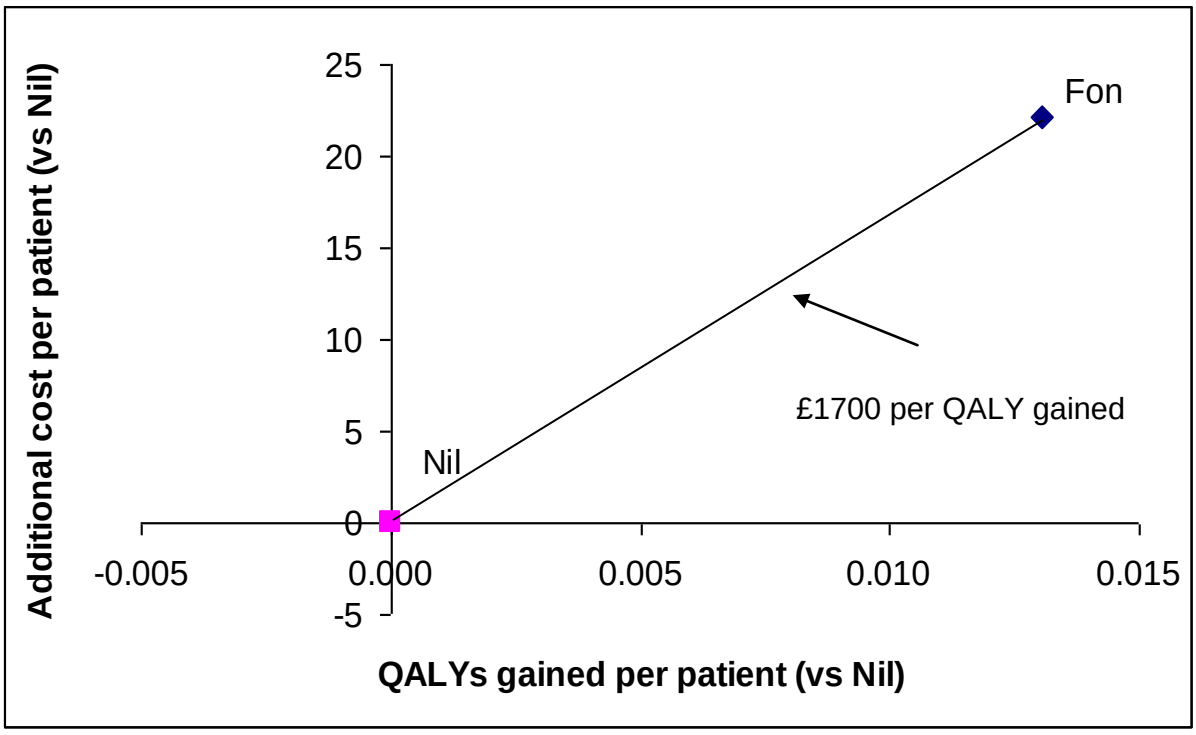

Figure 12-7: Base case results of the cost-effectiveness analysis for hip fracture patients: post-discharge prophylaxis
Fon = fondaparinux

12.4.4 Deterministic sensitivity analysis

Table 12-82: Deterministic sensitivity analysis results

Factors changed within the Model	*Most Cost-effective Strategy*	
	Standard duration prophylaxis	*Post Discharge (fondaparinux vs nil)*
Base case	Fondaparinux	Fondaparinux
Base case (probabilistic)	Fondaparinux	Fondaparinux
Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome		
0% Chronic Thromboembolic Pulmonary Hypertension	Fondaparinux	Fondaparinux
0.5% Chronic Thromboembolic Pulmonary Hypertension	Fondaparinux	Fondaparinux
1% Chronic Thromboembolic Pulmonary Hypertension	Fondaparinux	Fondaparinux
0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome	Fondaparinux	Fondaparinux
High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)	Fondaparinux	Fondaparinux
Low Post Thrombotic Syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT)	Fondaparinux	Fondaparinux
Low cost for Post Thrombotic Syndrome	Fondaparinux	Fondaparinux
High cost for Post Thrombotic Syndrome	Fondaparinux	Fondaparinux
High cost for Chronic Thromboembolic Pulmonary Hypertension	Fondaparinux	Fondaparinux
Other Sensitivity Analyses		
Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.5%, UFH=5%)	Fondaparinux	N/A
Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)	Fondaparinux	N/A
Using population specific major bleeding relative risks	N / A	N/A
Low aspirin major bleeding relative risk from Network Meta-analysis (RR = 0.49)	Fondaparinux	N/A
High aspirin major bleeding relative risk from aspirin vs. nil arms (RR = 1.3)	Fondaparinux	N/A
Discounted LMWH cost = £1	Fondaparinux	N/A
Fatality after PE = 10%	Fondaparinux	Fondaparinux
Fatality after Major Bleeding = 5%	Fondaparinux	Fondaparinux
Foot Impulse Devicecost (consumable: £40, pump: £0)	Fondaparinux	N/A
Increased NICE threshold (£30,000/ QALY)	Fondaparinux	Fondaparinux

QALY=quality-adjusted life-year

Table 12-83: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: standard duration prophylaxis

		Major bleeding risk												
PE risk	Fon	0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%	6%
	0%	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	0.5%	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	1%	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	1.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	2%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH	LMWH
	2.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH
	3%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH
	3.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH
	4%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	4.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	5.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	6%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon

Fon=fondaparinux,

Table 12-84: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: post-discharge

		Major bleeding risk												
PE risk		0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%	6%
	0%	Fon	Fon	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	0.5%	Fon	Fon	Fon	Fon	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	1%	Fon	Fon	Fon	Fon	Fon	Fon	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	1.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Nil	Nil	Nil	Nil
	2%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Nil	Nil
	2.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	3%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	3.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	4%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	4.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	5.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	6%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon

Fon=fondaparinux, Nil=no post-discharge prophylaxis

In a threshold sensitivity analysis, we found that post-discharge fondaparinux prophylaxis was no longer cost-effective if greater than 55% of patients require district nurse visits to deliver their prophylaxis.

12.4.5 Conclusion

For standard duration prophylaxis, fondaparinux was the most effective at increasing quality-adjusted life-years and the most cost-effective strategy.

For patients with a very low bleeding risk fondaparinux was the most cost-effective strategy. LMWH tended to be more cost-effective as the risk of major bleeding increased.

Fondaparinux was the most cost-effective strategy in all other deterministic sensitivity analyes conducted.

In the post discharge period fondaparinux was found to be cost-effective compared to no post-discharge prophylaxis. It remained the most cost-effective strategy in all of the deterministic sensitivity analyses conducted.

12.5 Patient views

No studies on patient views or adherence conducted specifically among patients undergoing hip fracture surgery were found.

For patient views from all patient groups (medical and surgical) about specific prophylaxis agents, see section 6.6**Error! Reference source not found.**.

12.6 Summary of evidence

Table 12-85: Summary of evidence from network meta-analysis results for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

Intervention(s)	**Comparison(s)**	**Intervention favoured**		
		DVT	**Mortality**	**MB**
Prophylaxis vs no prophylaxis				
IPCD/FID	no prophylaxis	Not sig	-	-
Fondaparinux	no prophylaxis	**Fondaparinux**	Not sig	**No prophylaxis**
LMWH	no prophylaxis	**LMWH**	Not sig	Not sig
UFH	no prophylaxis	**UFH**	Not sig	**No prophylaxis**
VKA (adjusted dose)	no prophylaxis	**VKA**	Not sig	Not sig
Aspirin (high-dose)	no prophylaxis	Not sig	Not sig	Not sig
IPCD then LMWH	no prophylaxis	**IPCD then LMWH**	-	-
Post Discharge **(from direct evidence)**				
Fondaparinux	No prophulaxis	**Fondaparinux**	Not sig	Not sig
Cost-effectiveness results				
Fondaparinux was the most cost-effective strategy for standard duration prophylaxis except when major bleeding rate risk was high in which case LMWH was most cost-effective.				
In the post discharge period fondaparinux was found to be cost-effective. No data were available for post-discharge use of LMWH in hip fracture patients.				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE ; or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. No event= outcomes reported in study(ies) but no events were reported. '-'= not reported. MB = Major bleeding

12.7 Recommendations and link to evidence

Recommendation	**Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing hip fracture surgery.** • **Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:** – **anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length).** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Provided there are no contraindications, add pharmacological VTE prophylaxis. Choose any one of:** – **fondaparinux sodium, starting 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2)** – **LMWH, starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.** – **UFH (for patients with renal failure), starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.** **Continue pharmacological VTE prophylaxis for 28-35 days, aaccording to the summary of product characteristics for the individual agent being used.**

Recommendation	**Fondaparinux sodium is not recommended for use preoperatively for patients undergoing hip fracture surgery. If it has been used preoperatively it should be stopped 24 hours before surgery and restarted 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2).**

Box 2-Bleeding Risk Factors	**Regard hospitalised patients as being at risk of bleeding if they have any of the following risk factors:** • **Active bleeding** • **Acquired bleeding disorders (such as acute liver failure)** • **Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)** • **Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours** • **Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours** • **Acute stroke** • **Thrombocytopenia (platelets < 75 x 10^9/l)** • **Uncontrolled systolic hypertension (230/120 mmHg or higher)** • **Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease).**

Relative values of different outcomes

The orthopaedic subgroup noted that although all-cause mortality is the most important outcome for this population the studies were not powered to detect a difference in mortality for any of the interventions under consideration. The next most important outcome was thought to be the risk of symptomatic venous thromboembolism balanced against the risk of major bleeding. The relative risk reduction for all DVT events was used as a surrogate for symptomatic VTE events as the orthopaedic subgroup accepted that there was a relationship between the risk reduction in DVT and PE.

Trade off between clinical benefit and

The benefit of reducing VTE events is balanced with the potential harms of bleeding. The economic model includes consideration of long-

harms

term sequelae such as the cost of reoperation due to bleeding, post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and stroke.
Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.

Economic considerations

An economic model was developed for this population. This model indicated that fondaparinux was the most effective and most cost-effective prophylaxis method for standard duration prophylaxis. LMWH was the next most-cost-effective strategy and became more cost-effective as the baseline risk of bleeding increases.

The economic model showed that extending prophylaxis with fondaparinux for 35 days post-surgery was cost-effective for this population. No data were available for determining the cost-effectiveness of extended LMWH prophylaxis used in this population, although results from elective hip replacement surgery indicated it was cost-effective for this population.

No evidence for combination prophylaxis in this population was included in the economic model. Evidence for the effectiveness of combination prophylaxis for fractures of the proximal femur is extrapolated from elective hip replacement evidence. As patients with fractures of the proximal femur have an increased DVT and PE risk compared with elective hip replacement surgery and that mechanical prophylaxis had no impact on the bleeding risk the orthopaedic subgroup felt that it was likely to be cost-effective in this population.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

The clinical evidence consisted of 30 RCTs of which 23 were included in the network meta-analysis for DVT. These studies tended to be small, 61% (14/23) and had less than 100 patients. In addition, 78% (18/23) were published before 1990. Some studies reported bleeding outcomes using different criteria. After a review of the techniques used for fixation of

the fractures of the proximal femur used within individual studies it was noted that there was a wide variety of techniques including some which were no longer used in current practice. This may limit the applicability of the evidence.

Other considerations

Many patients undergoing surgery for fracture of the proximal femur are likely to be elderly and may have comorbidities that increase the risk of developing deep vein thrombosis and pulmonary emboli.

Initiation of prophylaxis: The orthopaedic subgroup noted that in this population, individual patient risk factors for VTE (e.g. advanced age and immobility) were likely to be present at admission. It was also noted that surgery for these cases might not occur immediately due to time taken to stabilise the patient or availability of surgical resources. The orthopaedic subgroup agreed that prophylaxis should be initiated at admission once the bleeding risks had been established and it had been confirmed that patients did not have contraindications. The orthopaedic subgroup were concerned about pre-operative bleesding and noted that if the bleeding risks were unknown at admission, mechanical prophylaxis should be initiated until the risk of bleeding had been established.

The summary of product characteristics states a postoperative start time for dabigatran, rivaroxaban and fondaparinux, and a preoperative start time for most LMWHs although the actual start times vary depending on the specific LMWH. In this guideline it is recommended that LMWH is started postoperatively which is off-label because concerns about the risk of bleeding into the joint. Patients would be protected preoperatively against VTE by mechanical prophylaxis. Some of the LMWH studies included in our analyses also started LMWH postoperatively.

Use of fondaparinux: Although the results of the economic model found fondaparinux to be cost-effective both for standard duration and post discharge prophylaxis, the orthopaedic subgroup were aware of the increased risk of bleeding using this agent. Therefore, an additional statement was added to indicate that this agent should only be used where there was not an increased bleeding risk.

In addition, the orthopaedic subgroup decided that due to the longer acting duration of fondaparinux and therefore the need to stop it up to 24 hours before surgery, it should not be given as the preferred thromboprophylactic agent on admission.

Use of warfarin: The orthopaedic subgroup decided that warfarin should not be recommended for this population. Warfarin was felt to be an outdated modality, which was difficult to monitor. There were concerns with possible interactions between warfarin and other drugs and about lack of cost-effectiveness if continued after discharge.

Use of UFH: The Guideline Development Group felt that UFH should be considered as an option for patients with renal impairment.

Timing of chemical prophylaxis around surgery: The orthopaedic subgroup were mindful of the increase in bleeding risk in the period immediately after surgery. They suggested that prophylaxis with LMWH and UFH should be stopped 12 hours before surgery and recommenced once the immediate bleeding risk had reduced, 6-12 hours after the operation.

Mechanical prophylaxis: The orthopaedic subgroup noted that the use of anti-embolism stockings in patients with a fracture of the proximal femur after surgery was often painful and impractical but they felt that with care and following the recommendations relating to the use of stockings they could be used (section 6.7). The evidence demonstrates that IPCD/FID were cost-effective in this population compared with no prophylaxis and were likely to be a more practical solution than stockings in these patients.

Mechanical prophylaxis was felt to be particularly important in the period around the operation where patients were not protected by chemical prophylaxis. Likewise, if no pharmacological agents can be given for 24 hours then IPCD/FID should be provided at this time to ensure the patient has some protection from VTE events.

The orthopaedic subgroup were aware of patient compliance issues with the use of IPCD and anti-embolism stockings but agreed that they should be continued until the patient was

discharged or no longer had significantly reduced mobility.

Duration of prophylaxis: The cost-effectiveness results support the provision of fondaparinux for prophylaxis outside hospital. There is no evidence for extending the duration of LMWH after hip fracture surgery and so the recommendation for LMWH up to 35 days has been extrapolated from the evidence relating to elective hip replacement.

12.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing hip fracture surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information, including for post discharge prophylaxis (section 32.5)

12.8 Recommendations for research

Although not identified as a top 5 research recommendation (Chapter 2.3) the orthopaedic subgroup noted that the new oral anticoagulants (such as dabigatran and rivaroxaban) have not been trialed in patients undergoing hip fracture surgery. These drugs have the potential to make extended VTE prophylaxis much easier for patients with these patients as they are oral agents as opposed to requiring self injection (as LMWH does) and as such research in these patients would be beneficial.

12.9 Summary of recommendations

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing hip fracture surgery.
  - Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:
    - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Provided there are no contraindications, add pharmacological VTE prophylaxis. Choose any one of the following:

  - fondaparinux sodium, starting 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2),

  - LMWH, starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.

  - UFH (for patients with renal failure), starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.

  Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

➢ Fondaparinux sodium is not recommended for use preoperatively for patients undergoing hip fracture surgery. If it has been used preoperatively it should be stopped 24 hours before surgery and restarted 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2).

Box 2. Bleeding Risk Factors

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

13 Other orthopaedic surgery

13.1 Introduction

This section has been included to allow for a comprehensive review of the evidence available as it affects orthopaedic patients, mainly, in an elective setting. The populations covered are those undergoing upper limb surgery (including shoulders, elbows and hands), lower limb surgery (excluding elective total hip and knee replacement) and arthroscopy. There is some overlap with the section on lower limb plaster casts. Spinal surgery is not considered within this chapter (see section 14) It is difficult to be clear about the baseline risk of VTE as it affects these groups because of a lack of evidence but the incidence of DVT in the groups not receiving thromboprophylaxis of the RCTs identified for knee arthroscopy ranged between 4-15% and the effect may be magnified by the large number of patients involved.

The only available studies involve arthroscopy and, clearly, there are limitations in extrapolating from these data. However, the use of a risk assessment tool and a frank discussion with each patient at the pre-operative assessment clinic as part of the informed consent process about the pros and cons of prophylaxis is highly desirable. More complex procedures, for example, shoulder or elbow arthroplasty in a patient with rheumatoid arthritis, arthroscopically assisted ACL reconstruction or open ankle arthrodesis may be associated with a greater risk.

13.1.1 Spinal surgery

Spinal surgery can be completed by orthopaedic surgeons or neurosurgeons although there is a move to the same subspecialty practice in both specialties. Studies conducted in this population have often combined cranial and spinal surgery and it is difficult to separate the two. The evidence and recommendations for spinal surgery patients is presented in chapter 14 (Cranial and Spinal Surgery).

13.2 Evidence of methods of prophylaxis

13.2.1 Summary of comparisons identified for any outcome

The only population for which there was any evidence found was for knee arthroscopy, where 4 studies were identified [94,425,443,699].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

	Nil	Post-discharge	GCS	IPCDD/FID	Dabigatran	Fondaparinux	LMWH	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCDD/FID	Mech + pharm
GCS													
IPCDD/FID													
Dabigitran													
Fondaparinux													
LMWH	**2**	**1**	**1**										
UFH													
VKA													
High dose aspirin													
Low dose aspirin													
GCS + IPCDD/FID													
Mech + pharm													
Other comparisons													

Figure 13-37: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

13.2.2 Results from pairwise comparisons

Table 13-86: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[443,699]	2	2/183	15/186	0.014 (0.03, 0.61)	-0.08 (-0.20, 0.04)	ET: 26 FP: 13
Single proph vs single						
GCS vs LMWH [94]	1	29/660	10/657	2.89 (1.42, 5.88)	0.03 (0.01, 0.05)	ET: 37 FP: 81
Post discharge						
LMWH [425]	1	2/72	28/68	0.07 (0.02, 0.27)	-0.38 (-0.51, -0.26)	ET: 58 FP: 225

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*

Proph - prophylaxis

Table 13-87: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Single proph vs single						
GCS vs LMWH [94]	1	2/660	2/657	1.00 (0.14, 7.05)	0.00 (-0.01, 0.01)	ET: 37 FP: 81
Post discharge						
LMWH [425]	1	0/87	0/88	N/A	0.00 (-0.02, 0.02)	ET: 58 FP: 226

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 13-88: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[443,699]	2	0/183	0/186	N/A	0.00 (-0.01, 0.01)	ET: 26 FP: 15
Single proph vs single						
GCS vs LMWH [94]	1	1/660	2/657	0.50 (0.05, 5.48)	0.00 (-0.01, 0.00)	ET: 37 FP: 83
Post discharge						
LMWH [425]	1	0/87	0/88	N/A	0.00 (-0.02, 0.02)	ET: 58 FP: 230

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

13.2.3 Additional information

13.2.3.1 All cause mortality

None of the studies reported all cause mortality. Mortality is likely to be extremely rare after knee arthroscopy. In the elective knee replacement patients, estimating a mortality rate of 0.5% a power calculation estimated that 300,000 participants in each arm were required in order to detect a statistically significant difference between interventions (Chapter 1). As the mortality rate in knee arthroscopy patients is likely to be even lower than knee replacements, an even greater number of participants would be required to detect a difference.

13.2.3.2 Additional outcomes

No RCTs or systematic reviews reported results for post thrombotic syndrome, chronic thromboembolic pulmonary hypertension, heparin induced thrombocytopenia, quality of life or length of stay as outcomes for this population.

13.3 Network meta-analysis results

No network meta-analysis was completed for this population.

13.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

13.5 Patients view

No patient views or adherence studies conducted specifically among the patient groups discussed in this chapter was identified. However, there are studies conducted in patients with hip replacement, knee replacement, lower limb plaster casts, and general surgery (Chapter 10 - 1, 21 and 9 respectively).

For patient views about specific prophylaxis agents, see section 6.6.

13.6 Summary of evidence

Table 13-4: Summary of evidence from direct evidence for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
LMWH	No prophylaxis	**LMWH**	NR	Not sig
Single prophylaxis vs. single				
LMWH	GCS	**LMWH**	Not sig	Not sig
Post Discharge				
LMWH	No prophylaxis	**LMWH**	Not sig	Not sig
Cost Effectiveness				
There is no relevant cost-effectiveness evidence specifically for this population subgroup.				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.
Not sig - not statistically significant difference; NR – not reported; no events – nobody in the study had the outcome. MB = Major bleeding

13.7 Recommendations and link to evidence

Recommendation	**Consider offering combined VTE prophylaxis with mechanical and pharmacological methods to patients having orthopaedic surgery (other than hip fracture, hip replacement, knee replacement) based on an assessment of risks (see section 5.9) and after discussion with the patient.** • **Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:** – **anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length).** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Start pharmacological VTE prophylaxis 6–12 hours after surgery. Choose one of:** – **LMWH** – **UFH (for patients with renal failure).** **Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.**
Recommendation *(From section 5.9)*	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 – VTE risk factor box	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory**

	pathologies, acute infectious diseases or inflammatory conditions) • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.
Economic considerations	No cost-effectiveness analysis was conducted for this group of patients. This is a potentially large population, and recommending prophylaxis may have significant impact on NHS costs. Patients in this population are relatively young compared to other groups, and any fatal VTE or fatal bleeding events, or long term events due to thrombosis or bleeding could result in a higher loss of quality adjusted life years than the populations where cost-effectiveness analysis has been conducted. However, the risk of pulmonary embolism is probably quite low compared with other groups, especially for patients having surgery on the upper limbs. Therefore it is unlikely that prophylaxis will be cost-effective unless patients have additional risk factors.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). The evidence for this population is weak, consisting of only 4 RCTs in knee arthroscopy patients. The incidence of DVT in the studies varied and the overall incidence of PE was very low, 0.3% in the trial comparing LMWH with GCS, and there was no evidence from this population that prophylaxis reduced the risk of these events.
Other considerations	Although the orthopaedic subgroup felt that many of the patients undergoing orthopaedic surgery in the upper limb, lower limb and arthroscopy other than elective hip replacement, elective knee replacement and hip fracture surgery would not require

prophylaxis, they did acknowledge that there may be a subgroup of these patients who were at increased risk of VTE and so should be offered the opportunity for prophylaxis. The factors that identify a patient at high risk are given in the recommendation for assessing VTE risk above. The orthopaedic subgroup felt that if any of these conditions were met then prophylaxis should be considered.

Although there is only evidence for prophylaxis with LMWH in knee arthroscopy patients, the orthopaedic subgroup felt that the evidence for fondaparinux from elective hip replacement, hip fracture and knee replacement surgery could be extrapolated for this population.

Similarly mechanical methods such as anti-embolism stockings or intermittent pneumatic compression devices can be used in conjunction or as an alternative to pharmacological prophylaxis.

13.7.1 Supporting recommendations based on Guideline Development Group consensus opinion

Recommendation	**Do not routinely offer VTE prophylaxis to patients undergoing upper limb surgery. If a patient is assessed to be at increased risk of VTE (section 5.9) refer to recommendation from other orthopaedic surgery (above in section 13.7).**
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.
Economic considerations	No cost-effectiveness analysis was conducted for this group of patients. This is a potentially large population, and recommending prophylaxis may have significant impact on NHS costs. Patients in this population are relatively young compared to other groups, and any fatal VTE or fatal bleeding events, or long term events due to thrombosis or bleeding could result in a higher loss of quality adjusted life years than the populations where cost-effectiveness analysis has been conducted. However, the risk of pulmonary embolism is probably very low especially for patients having surgery on the upper limbs compared with other groups. Therefore it is unlikely that prophylaxis will be cost-effective unless patients have additional risk factors.
Other considerations	The feedback from stakeholder consultation indicated that the initial draft of the guideline did not make it clear that many patients undergoing upper limb surgery would not need VTE prophylaxis. Stakeholders raised the issue that no studies of prophylaxis had been completed in upper limb surgery and that the studies of incidence of VTE after this type of surgery indicated that the risk was very small.

In order to make the recommendations clearer, the orthopaedic subgroup agreed that a separate recommendation should be included to clarify this. The orthopaedic subgroup agreed that although most patients undergoing upper limb surgery would not need VTE prophylaxis all patients should still be risk assessed as recommended in section 5.9 and if there were patients who were at an increased risk VTE prophylaxis should still be considered.

13.7.2 Other recommendations of relevance

The specific recommendations for patients undergoing orthopaedic surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)

13.8 Recommendations for research

Dabigatran and rivaroxaban are not licensed for this population but are oral anticoagulants that are licensed for hip and knee replacement patients. This might be an area for future research in this population, particularly where patients are identified to be at increased risk and have a lower limb plaster cast.

13.9 Summary of recommendations

- Consider offering combined VTE prophylaxis with mechanical and pharmacological methods to patients having orthopaedic surgery (other than hip fracture, hip replacement or knee replacement) based on an assessment of risks (see section 5.9) and after discussion with the patient.
    - Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:
        - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
        - foot impulse devices
        - intermittent pneumatic compression devices (thigh or knee length)

      Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
    - Start pharmacological VTE prophylaxis 6–12 hours after surgery. Choose one of:
        - LMWH

- UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - have one or more risk factors in **Box 1.**

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

- Do not routinely offer VTE prophylaxis to patients undergoing upper limb surgery. If a patient is assessed to be at increased risk of VTE (section 5.9) refer to section 13.7.

17 Day-case surgery

17.1 Introduction

This section covers patients undergoing procedures as a day-case. It will cover a wide range of procedures across many of the specialities. For the purpose of this guideline, patients are considered as day-cases their procedures meet one of the following three criteria described by the British Association of Day Surgery[84]:

- Procedure room – operation that may be performed in a suitable clean environment outside of theatres
- Day-case – "traditional day surgery"
- 23 hour stay – patients admitted and discharged within 24 hours

Special considerations for VTE

- day-case patients are likely to be more mobile and on average, younger than patients admitted for an in-patient stay.

There are no special considerations for bleeding in this group

17.2 Evidence of methods of prophylaxis

No studies were identified that investigating VTE prophylaxis in day-case surgery patients.

17.3 Network meta-analysis results

Network meta-analysis was not completed for this population

17.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

17.5 Patient views

No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.

17.6 Summary of evidence

There is no RCT evidence covering prophylaxis in patients having day-case surgery.

17.7 Recommendations and link to evidence

Recommendation	**Offer VTE prophylaxis to patients undergoing day surgery who are assessed to be at increased risk of VTE (see section 5.9)** • **Start mechanical VTE prophylaxis at admission. Choose any one of:** – **anti-embolism stockings (thigh or knee length)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length)** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose one of:** – **LMWH** – **UFH (for patients with renal failure).** **If the patient is expected to have significantly reduced mobility after discharge, continue pharmacological VTE prophylaxis for generally 5-7 days.**
Recommendation from section 5.9	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 – VTE Risk factor box	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias**

	• **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The outcomes considered for the review were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. These trade offs were considered to be similar to those for patients admitted to hospital for surgery. Should an individual risk factor exist then the patient would still be considered at risk of developing VTE.
Economic considerations	There is no relevant cost-effectiveness evidence specifically for this population subgroup. However, a combination of drug and mechanical prophylaxis was found to be cost-effective for general surgery patients where the risk of major bleeding is less than 1%. It seems likely that combination prophylaxis will also be cost-effective for day-case surgery patients who are at elevated risk of VTE and who have a moderate risk of major bleeding.
Quality of evidence	No evidence was identified specifically in this population.
Other considerations	The GDG discussed the use of prophylaxis in this population. Although they acknowledged that some day case patients may be younger and more mobile than patients undergoing the same type of surgery as an inpatient, this is not necessarily the case. They felt that the increase in the number of day case procedures completed may result in more complex surgery being completed on a day case basis and that there was the potential for patients to be discharged from hospital only for them to have an extended periods of signficiantly reduced mobility at home. They agreed that the principle of risk

assessment for all patients VTE was key.

The average duration of VTE prophylaxis for 'general surgery' patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. The guideline development group felt that the risk of VTE may still persist beyond discharge and post-discharge prophylaxis may be effective in some cases. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

17.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing day-case surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- The use of local anaesthesia by local infiltration with no reduction in mobility (Section 19.4)
- risk assessment for VTE and major bleeding (Section 5.9)
- the use of VTE prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)

17.8 Summary of recommendations

- Offer VTE prophylaxis to patients undergoing day surgery who are assessed to be at increased risk of VTE (see section 5.9)
    - Start mechanical VTE prophylaxis at admission. Choose any one of:
        - anti-embolism stockings (thigh or knee length)
        - foot impulse devices
        - intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantlt reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose one of:

  - LMWH

  - UFH (for patients with renal failure).

  If the patient is expected to have significantly reduced mobility after discharge, continue pharmacological VTE prophylaxis for 5-7 days.

- Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - have one or more risk factors shown in **Box 1**.

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum)..