



Emergency Department

Guidelines in Emergency Medicine Network - GEMNet

Guideline for the use of thromboprophylaxis in ambulatory trauma patients requiring temporary limb immobilisation

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About this guideline

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1. Executive summary

- The Guidelines in Emergency Medicine Network (GEMNet) has been created to promote best medical practice in a range of conditions presenting to Emergency Departments (EDs) in the UK.
- This guideline presents a summary of the best available evidence to guide the use of thromboprophylaxis in adult ambulatory outpatients who present to the ED following acute limb trauma and require temporary immobilisation.
- The document has been developed following discussion amongst Emergency Physicians and collegiate fellows to decide which topics would benefit from the development of clinical guidelines.
- The document is intended as a guideline for use in the ED by Emergency Physicians and is based on the review of the best existing evidence for treatments used in this setting.
- The document is summarised as a Clinical Decision Support Guideline that has been presented as an easy to follow algorithm.
- The intention is for each guideline to be updated and reviewed as further evidence becomes available. The formal revision date has been set at 5 years from publication though the guideline is subject to continuous informal review.

2. Introduction

2.1 Responsibility for development

This document has been developed in response to a perceived need to improve clinical effectiveness for care in this field, in addition to the call for routine risk assessment through recent NICE guidance (1). The intention is to distil information from the medical literature into practical advice for clinicians working in the department. The information is presented in the form of a Clinical Decision Support Guideline, available on the shop floor in the form of a Clinical Decision Support Manual and on individual A4 sized forms.

2.2 Funding

Funding for the development of this guideline was received from the College of Emergency Medicine.

2.3 The guideline working group

A Guideline Working Group met to discuss this condition and decide on the clinical questions, consider the evidence available and develop the recommendations. Due process ensured that the working group had access to the relevant information and the required resources in order to develop in a constructive manner.

The guideline has been developed in accordance with the principles described by the National Institute for Health and Clinical Excellence guideline development methods (2).

3. Topic introduction

The relationship between temporary limb immobilisation and venous thromboembolism (VTE) has been documented since 1944 (3). This link persists despite modern medical care, with lower-limb immobilisation recently implicated as an aetiological factor in approximately 1.5 -3% of all VTE events (4, 5). The actual incidence of VTE in patients with temporary plaster immobilisation is estimated anywhere between 5 - 39%, depending on the type of patient and the type of immobilisation (6-10). When compared to an annual VTE incidence of 0.12-0.18% in a normal undifferentiated population, these figures serve as a stark reminder of risk (11-13).

The concept of prescribing thromboprophylaxis to ambulatory patients in temporary immobilisation is not a novel one. Prophylaxis is commonplace in some European countries (14-15), being recommended in national guidance from both the French and German Medical Societies (17). However, contemporary literature would suggest that UK and American practice does not mirror that seen within Europe. A recent UK national survey indicates that over 60% of departments do not routinely use thromboprophylaxis. In those that do there is little agreement as to the practicalities of administration (18, 19).

The lack of consensus decision making for this cohort is likely, in part, due to an absence of clear guidance. Although the Department of Health recently highlighted VTE prevention as a clinical priority, implementing a national programme (20) and producing National Institute of Clinical Excellence (NICE) guidelines regarding the indications and use of thromboprophylaxis in inpatients (1), advice regarding outpatient therapy is scant. In relation to the use of thromboprophylaxis in patients with temporary immobilisation, guidance is limited to a single sentence, which provides no practical advice for shop floor clinicians.

A further barrier to consideration and implementation stems from the failure to recognise VTE as a significant problem within this cohort of patients. There is evidence to suggest clinicians often consider serious VTE to be rare within this group, despite regular published reports within the medical literature (21, 22) and national media (23, 24). Additionally, a significant proportion of VTE events documented following temporary immobilisation are distal calf thrombi (9, 25, 26). Equipose remains regarding the management of distal DVT (27, 28). However, this does not mean that the condition is without risk of serious morbidity. Propagation rates as high as 39% have been demonstrated with conservative management, and embolisation has been reported within a single week (29, 30). In addition a real potential of subsequent post-thrombotic syndrome exists (31).

This guideline seeks to address the gap in UK national guidance, applicable to Emergency Physicians, with regards to the use of thromboprophylaxis in ambulatory trauma patients with temporary limb immobilisation. We aim to summarise and distil the relevant evidence with regards to the prevention of VTE in this cohort of patients, with the goal of providing a structured treatment pathway, and this has been presented as a series of clinical questions, which have been answered using the previously described Best BETs methodology (32).

This guideline does not aim to replace previous advice but to present a complementary structure guideline and evidence-based flowchart to aid the decision-making process for these patients within the ED. It is hoped that this will help to optimise and standardise the care delivered to this group.

4. Scope

This guideline encompasses adult patients (>16 years of age) presenting to the ED with ambulatory limb trauma suitable for temporary limb immobilisation and community follow up. The guideline excludes all hospital inpatients, the majority of whom will be prescribed thromboprophylaxis as standard. The key aspects of the guideline include evidence based assessment of the incidence and nature of VTE, individualised risk assessment, prophylaxis options and risks associated with prophylactic anticoagulation. The initial assessment and management recommendations can be followed using resources available in any UK ED. Disposition, follow up and ongoing care may vary dependent on local resources but the guideline may be adapted as appropriate.

This document does not provide guidance regarding patients less than 16 years of age, patients with multiple injuries, hospital inpatients or those with complex haematological issues. The use of physical or limited availability treatments such as intermittent pneumatic compression devices is also excluded because of limited availability throughout the country and applicability to the patient with lower limb immobilisation.

5. Methodology

This guideline was developed using a novel methodology that has recently been utilised in cardiothoracic surgery (33). Many guidelines perform a single systematic review of the literature in order to answer all of the relevant clinical questions. In order to maximise sensitivity, we performed a separate short-cut systematic review of the literature for each clinical question identified.

Guideline development was structured into several stages. Initially the two lead guideline developers (CR and DH) met to discuss the scope of the guideline and to identify all clinical questions that may have been relevant. To answer the clinical questions identified we performed a series of structured short-cut systematic reviews (Best BETs), the principles of which have been previously described (32).

Having gathered and collated the evidence for each clinical question, the principle guideline developers met to create a series of guideline recommendations, which were used to create an evidence-based flowchart. Following consultation with the senior author (KMJ), modifications were made before the final guideline was agreed upon.

5.1 Levels of evidence and grading of recommendations

Studies included in this guideline were graded for level of evidence according to previously accepted definitions (34). In summary, level 1 evidence comes from well-designed randomised controlled trials (RCTs), level 2 evidence from large cohort studies or poorly designed RCTs, level 3 evidence from small cohort studies or case-control studies and level 4 evidence from experimental studies, case series or case studies. The suffix 'a' implies that evidence at this level is from systematic review or meta-analysis, whereas the suffix 'b' implies that the evidence is from original research.

The recommendations that have been made were graded according to the level of evidence upon which they were based:

Grade A: Based upon multiple level 1a or 1b papers.

Grade B: Based upon individual level 1a or 1b papers or multiple level 2a or 2b papers.

Grade C: Based upon individual level 2a or 2b papers or multiple level 3a or 3b papers.

Grade D: Based upon individual level 3a or 3b papers or level 4 papers.

Grade E: Based on consensus guidelines or studies of expert opinion.

5.2 Definitions of thromboprophylaxis and immobilisation

For the purposes of this guideline, thromboprophylaxis is defined as any anticoagulant therapy administered by any route at a dose considered to be prophylactic, rather than therapeutic, for the patient concerned.

Immobilisation is defined as any clinical decision taken to manage the affected limb in such a way as to prevent normal weight bearing status and/or use of that limb.

Transient/temporary risk refers to a provoking risk factor, with a definitive temporal association. Permanent risk refers to an ongoing risk factor with no definitive time period of association, or clear cessation date.

Venous thromboembolism (VTE) refers to a composite outcome, including any of distal deep vein thrombosis, proximal deep vein thrombosis, central venous thrombosis and pulmonary embolism.

6. Summary of recommendations

6.1 The risk of VTE in upper limb immobilisation

There is no evidence to suggest a significant risk of VTE in ambulatory patients with isolated injury and temporary upper limb immobilisation. (**Grade C**)

6.2 The risk of VTE in lower limb immobilisation

There is reasonable evidence to suggest a significant risk of VTE in ambulatory patients with isolated injury and subsequent temporary lower limb immobilisation. (**Grade A**)

6.3 Assessing individual risk in the Emergency Department

No validated clinical prediction score exists to enable protocolised risk assessment in ambulatory patients with temporary limb immobilisation. **(Grade E)**

Ambulatory patients with lower limb immobilisation and any of the following temporary risk factors should be considered to be at increased risk of venous thromboembolic disease:

Rigid immobilisation

Non-weight bearing status

Acute severe injury (dislocation, fracture or complete tendon rupture) **(Grade C)**

Combination of 2 or more risk factors for venous thromboembolism in patients with isolated limb injury increase the risk of developing subsequent VTE. **(Grade C)**

6.4 Who stands to benefit from thromboprophylaxis

There is no evidence to suggest that ambulatory patients with lower limb injuries immobilised in splints will benefit from routine thromboprophylaxis. **(Grade C)**

There is evidence to support the use of thromboprophylaxis in ambulatory patients with isolated limb injury who are immobilised in below knee plaster cast. **(Grade A)**

There is evidence to support the use of thromboprophylaxis in ambulatory patients with isolated limb injury who are immobilised in above knee plaster cast. **(Grade C)**

Thromboprophylaxis should be strongly considered for ambulatory patients with lower limb injury and temporary risk (see above), in addition to any permanent additional risk factor for venous thromboembolic disease. **(Grade C)**

6.5 Types and duration of thromboprophylaxis

Current evidence investigating oral anticoagulants is too limited to allow recommendation of any oral therapy as thromboprophylaxis for ambulatory patients with temporary lower limb immobilisation. **(Grade B)**

When indicated, the use of prophylactic low molecular weight heparin (LMWH) is effective at reducing incidence of VTE in ambulatory patients with lower limb immobilisation. **(Grade A)**

If commenced, prophylactic LMWH should be given for the duration of the plaster immobilisation period. **(Grade E)**

6.6 Risks associated with thromboprophylaxis

The use of prophylactic LMWH is associated with low rates of heparin induced thrombocytopenia and major bleeding when used for thromboprophylaxis in ambulatory patients with plaster cast immobilisation. **(Grade A)**

7. Evidence for recommendations

Below are summaries of the short cut systematic reviews used to establish the recommendations for this guideline. The three part question and search details are presented with comments and clinical bottom line.

7.1 The risk of venous thromboembolic disease (VTE) in upper limb immobilisation

Assessing whether ambulatory patients with temporary upper limb immobilisation are at an increased risk of VTE.

Three part question

In [patients with isolated upper extremity injury] does [the use of temporary immobilisation via plaster cast/sling] increase the risk of [subsequent venous thromboembolic events during short term follow up]?

Search strategy

Cochrane database week ending 13th May 2011

MEDLINE and EMBASE via NHS evidence week ending 13th May 2011

[(exp IMMOBILIZATION) OR (exp CASTS, SURGICAL) OR (exp SPLINTS) OR (sling.ti,ab) OR (cast*.ti,ab) OR (immobilisation.mp) OR (plaster AND of AND paris.mp) OR (back-slab.ti/ab)] AND [(exp UPPER EXTREMITY) OR (upper AND extremity.ti,ab) OR upper AND extremity.ti,mp) OR (arm.ti,ab) OR (exp ARM INJURIES) OR (exp HAND) OR (exp HAND INJURIES) OR (exp FINGER) OR (exp FINGER INJURIES) OR (exp SHOULDER DISLOCATION) OR (exp FRACTURES, BONE)] AND [(exp VENOUS THROMBOEMBOLISM) OR (exp THROMBOEMBOLISM) OR (exp PULMONARY EMBOLISM) OR (exp DEATH, SUDDEN) OR (exp VENOUS THROMBOSIS) OR (exp THROMBOPHLEBITIS) OR (VTE.ti,ab) OR (deep AND vein AND thrombosis.mp) OR (pulmonary AND embolism.mp) OR (thrombo*.ti,ab) OR (exp RISK FACTORS) OR (*UPPER EXTREMITY DEEP VEIN THROMBOSIS/co) OR (*UPPER EXTREMITY DEEP VEIN THROMBOSIS/di)]

Search outcome

In total 104 papers were identified of which 4 were felt to be relevant to the three part question.

Comments

In total four studies relevant to the clinical question were identified: three retrospective cohort studies (35-37) and one case control study (38). All of these are relatively small and none were designed to directly test an association between temporary upper limb immobilisation and upper limb DVT.

Clinical bottom line

There is currently no evidence to suggest that temporary upper limb immobilisation is associated with an increased risk of upper limb DVT.

Recommendation

There is no evidence to suggest a significant risk of VTE in ambulatory patients with temporary upper limb immobilisation (**Grade C**).

7.2 The risk of venous thromboembolic disease (VTE) in lower limb immobilisation

Assessing whether ambulatory patients with temporary lower limb immobilisation are at an increased risk of VTE.

Three part question

In [non-surgical ambulatory patients with isolated lower limb injury] does [temporary immobilisation] increase the three-month risk of [venous thromboembolic disease or sudden death]

Search strategy

MEDLINE was searched using the OVID Interface from 1948 to July Week 1 2011. EMBASE was searched using the OVID Interface from 1980 to 2011 Week 27.

The Cochrane Database of Systematic Reviews was also searched using direct terminology applicable to the three part question.

(exp IMMOBILIZATION/) OR (exp CASTS, SURGICAL/) OR (exp SPLINTS/) OR (immobilisation.ti,ab) OR (immobilisation.mp) OR (plaster AND of AND paris.mp) OR (plaster AND of AND paris.ti,ab) OR (plaster AND cast.ti,ab) OR (backslab.ti,ab) OR exp Splints/] AND [(lower AND limb.ti,ab) OR (lower AND limb.mp) OR exp LEG/ OR exp Lower extremity/] AND [(exp VENOUS THROMBOEMBOLISM/) OR (exp THROMBOEMBOLISM/) OR exp Deep Vein Thrombosis/ OR (exp PULMONARY EMBOLISM/) OR (deep AND vein AND thrombosis.mp) OR (pulmonary AND embolism.mp) OR (VTE.ti,ab) OR (exp DEATH, SUDDEN)]

Search outcome

124 papers retrieved of which 4 were directly relevant to the three part question [34,35,37,39].

Comment(s)

Temporary immobilisation in non-surgical isolated limb trauma within the preceding two months has been recently associated with 2% of all venous thromboembolic events (4). These events can be potentially fatal. Limb immobilisation has also recently been highlighted as provoking the highest risk of VTE among all causes of immobilisation (39). National guidance promotes clear advice regarding thromboprophylaxis in hospital inpatients. There is little advice regarding ambulatory patients seen in the emergency department who are exposed to similar risk. To address the issue properly we must first understand the scale of the problem, by identifying the incidence of disease in order to quantify risk. There are several common issues regarding the majority of studies generating data within the designated cohort. Firstly, the use of VTE event as an outcome generates controversy: an event can range from an isolated asymptomatic distal DVT to a life threatening PE. Some would argue that these events have profoundly differing morbidity/mortality rates and as such should not be collated as an outcome. Secondly,

many studies group post surgical ambulatory together with conservatively treated patients. This can distort the Emergency Department cohort and should be carefully avoided when addressing epidemiological questioning.

Clinical bottom line

The incidence of VTE following temporary immobilisation for isolated lower limb trauma in ambulatory patients is approximately 11%. This rate can vary in different ambulatory cohorts from 5 to 30%, depending on the type of injury and immobilisation used. Although the majority of these events will be distal DVT, pulmonary emboli do occur in this cohort and contribute to total incidence.

Recommendation

There is good evidence to suggest a significant risk of VTE in ambulatory patients with temporary lower limb immobilisation (**Grade A**).

7.3 Assessing individual risk in the Emergency Department

Can individual assessment be used to predict VTE risk in the emergency department for patients with isolated limb trauma and temporary immobilisation?

Three part question

In [patients with lower extremity injury requiring temporary immobilisation] can [risk assessment/stratification] predict [likelihood of venous thromboembolic events within the subsequent 3 months]?

Search strategy

Cochrane database and MEDLINE/EMBASE were searched to the week ending Friday 13th May 2011, using NHS evidence as an interface.

(exp IMMOBILIZATION/) OR (exp CASTS, SURGICAL/) OR (exp SPLINTS/) OR (immobilisation.ti,ab) OR (immobilisation.mp) OR (plaster AND of AND paris.mp) OR (plaster AND of AND paris.ti,ab) OR (plaster AND cast.ti,ab) OR (backslab.ti,ab)] AND [(lower AND limb.ti,ab) OR (lower AND limb.mp) OR exp LEG/] AND [(exp VENOUS THROMBOEMBOLISM/) OR (exp THROMBOEMBOLISM/) OR (exp PULMONARY EMBOLISM/) OR (deep AND vein AND thrombosis.mp) OR (pulmonary AND embolism.mp) OR (VTE.ti,ab) OR (exp DEATH, SUDDEN)]

Search outcome

1 Cochrane review was deemed directly relevant to the three part question (9). However, this article contained no information regarding quantification of risk factors or prediction of risk for VTE. It was therefore discarded from the final analysis.

148 papers were identified and reviewed by title and abstract. Only 4 of these papers were deemed directly relevant to the three part question (40-43). These papers are included in the table of evidence below:

Comments

No formal validated decision rule/risk assessment tool is currently available to allow stratification of thromboprophylaxis in ambulatory emergency department patients with temporary lower limb immobilisation. However, work has been done to identify contributory risk factors for the development of VTE during immobilisation and determine

those patients most likely to benefit from thromboprophylaxis. Scoring systems based on these data and expert opinion are currently in use within the UK (Plymouth VTE trauma score), designed to approximate levels of risk and advise on thromboprophylaxis accordingly. These scores are in urgent need of validation prior to regional or national adoption. The largest study (2761 patients) addressing risk factors for the development of VTE in immobilised non-surgical isolated lower limb injuries used multivariate analysis to define predictive variables for VTE [40]. The authors list age >50, rigid immobilisation, non-weight bearing status and severe injury (fracture/dislocation/complete tendon rupture) all individually resulting in an OR >1.8. Smaller previous studies support these data, noting a much lower incidence of VTE in young, low risk, weight bearing cohorts with predominate soft tissue injuries (8, 41). These individual factors can thus immediately be used to highlight a cohort at increased risk for VTE. How much risk is worthy of routine prophylaxis? This is unfortunately where a dearth of high quality evidence exists. Kujath et al noted a mean of two risk factors present in patients with lower limb immobilisation developing deep vein thrombosis and 2.7 risk factors in those developing VTE despite prophylaxis (42). Both figures were statistically significant compared to quantitative risk factors in those patients not developing VTE. Thus, the presence of any additional known risk factor in tandem with the above risk group imply a need for prophylaxis. In support of this approach are the data regarding the safety of prophylactic low molecular weight heparin (LMWH) in ambulatory patients with temporary immobilisation. A recent Cochrane Review reported an incidence of major bleeding of <0.3%, with no cases of heparin induced thrombocytopenia noted in 750 patients (9). A subsequent systematic review also noted no significant risk of major or minor bleeding in over 700 patients treated with LMWH prophylaxis, when compared to a similar number treated with placebo (RR 1.22, 95% CI 0.61 to 2.46, p=0.57) (44). These data suggest that in the majority of 'at risk' patients, the benefits of prophylaxis are indeed likely to outweigh the potential harms.

Clinical bottom line

Ambulatory patients with temporary lower leg immobilisation who are in a rigid cast, non-weight bearing or with a severe injury should be considered as an at risk group for VTE. If there are any other current proven VTE risk factors, patients should be considered as high risk.

Recommendations

No validated clinical prediction score exists to enable protocolised risk assessment in ambulatory patients with temporary limb immobilisation. **(Grade E)**

Ambulatory patients with lower limb immobilisation and any of the following temporary risk factors should be considered to be at increased risk of venous thromboembolic disease:

Rigid immobilisation

Non-weight bearing status

Acute severe injury (dislocation, fracture or complete tendon rupture). **(Grade C)**

Combination of 2 or more risk factors for venous thromboembolism in patients with isolated limb injury increase the risk of developing subsequent VTE. **(Grade C)**

7.4 Who stands to benefit from thromboprophylaxis

- a. Patients temporarily immobilised in splints / wool and crepe dressings
- b. Patients temporarily immobilised in above knee plaster cast
- c. Patients temporarily immobilised in below knee plaster cast

7.4a Patients temporarily immobilised in splints / wool and crepe dressings

Three part question

In [patients with knee injuries requiring immobilisation in a cricket pad splint] does [prophylactic anticoagulation with LMWH] reduce the risk of [venous thromboembolic disease over the subsequent three months]?

Search strategy

MEDLINE and EMBASE databases via the OVID interface the week ending the 24th June 2011

MEDLINE: (exp venous thrombosis OR exp thromboembolism OR exp pulmonary embolism OR DVT.mp OR deep vein thrombosis.mp OR PE.mp OR pulmonary embolism.mp OR venous thromb\$.mp) AND (exp splint OR splints.mp OR cricket pad splint.mp OR exp immobilization OR immobilization.mp)

EMBASE: (exp vein thrombosis OR exp thromboembolism OR exp lung embolism OR exp venous thromboembolism OR exp deep vein thrombosis OR DVT.mp OR deep vein thrombosis.mp OR PE.mp OR pulmonary embolism.mp OR venous thromb\$.mp) AND (exp splint OR splints.mp OR cricket pad splint.mp OR exp immobilization OR immobilization.mp)

Both searches were limited to human subjects only.

Search outcome

In total 401 and 1221 papers were found in the MEDLINE and EMBASE searches respectively. None of which were felt to be relevant to the three part question.

Comments

No trials investigating the relationship between venous thromboembolism and immobilising splints exist. One study by Lassen et al (26) does include patients treated with 'braces'. However, the authors do not specify the type of brace use, the numbers included are small and there is no pre-specified subgroup analysis performed on this cohort.

Clinical bottom line

There is no evidence demonstrating that ambulatory patients with lower limb injuries immobilised in splints are at an increased risk of venous thromboembolism.

Recommendation

Routine thromboprophylaxis should not be given to partially weight bearing patients with knee injuries immobilised in splints. (Grade C)

7.4b Patients temporarily immobilised in below knee plaster casts

A previously published short cut review on this topic (45) was updated.

Three part question

In [ambulatory patients with acute lower extremity injury requiring temporary immobilisation with below-knee plaster cast] does [prophylactic dose anticoagulation with LMWH] reduce the risk of [venous thromboembolic disease within 90 days]

Search Strategy

MEDLINE and EMBASE via the Ovid interface, the week ending the 5th June 2011.

MEDLINE: (exp venous thrombosis OR exp thromboembolism OR exp pulmonary embolism OR DVT.mp OR deep vein thrombosis OR PE.mp OR pulmonary embolism.mp OR venous thromb\$.mp) AND (exp casts surgical OR plaster cast\$.mp OR exp immobilization OR immobilisation.mp)

EMBASE: (exp vein thrombosis OR exp thromboembolism OR exp lung embolism OR exp venous thrombosis OR exp deep vein thrombosis OR DVT.mp OR deep vein thrombosis.mp OR PE.mp OR pulmonary embolism.mp OR venous thromb\$.mp) AND (exp plaster cast OR exp immobilization OR plaster cast\$.mp OR immobilisation.mp)

All searches were limited to human subjects only.

Search outcome

439 and 1280 records were found in the MEDLINE and EMBASE searches respectively. Following an initial review 14 of these were thought to be relevant to the three part question. However, 9 of these were subsequently rejected as they dealt with surgically managed patients or duplicated studies reported elsewhere. This left 4 RCTs and a Cochrane review. All four of the RCTs were included in the Cochrane review and therefore this was considered as the best evidence available (9).

Comments

The use of thromboprophylaxis in ambulatory patients with plaster cast immobilisation, is commonplace in most European countries. Current UK use is minimal, likely as a result of recent national guidance failing to give clear recommendations. Since the original BET on this topic in 2007 (45), there have been three systematic reviews published (9, 44, 46). Two of these include post-operative orthopaedic surgical ambulatory patients within the analysis (44, 46) and are thus limited in their applicability to an emergency medicine cohort. The Cochrane review cited above however, does subgroup non-surgical patients to address specific risk within the conservatively managed outpatient group. The evidence presented suggests that the use of thromboprophylaxis can significantly reduce the chance of a venous thromboembolic (VTE) event in patients with a below knee plaster cast and those conservatively treated. ARR varies between 6.8% and 7.1% in these groups. This data would suggest a NNT of 14 to prevent 1 event. Furthermore it is worth noting that all included studies within the meta-analysis exclude patient groups considered to be high risk for developing VTE; the rate of DVTs seen will likely underestimate that found in an undifferentiated emergency department population. However, the clinical significance of these results is uncertain. Despite the high rate of DVTs seen the majority (66 -100%) were asymptomatic and would therefore be unlikely to be detected in normal clinical practice. In addition pulmonary embolism was only seen in 0.3% cases and no deaths occurred within the untreated cohort. A high prevalence of

distal DVT serving as a positive outcome also generates debate regarding routine use; the rate of propagation, embolisation and post thrombotic syndrome seen to follow distal DVT remains poorly quantified (31). Although rates of HIT and major bleeding were low overall (<0.3%), concerns remain regarding the wider impact of generalised use. It is necessary to balance any benefit gained against the potential risk of increased bleeding with the use of LMWH. Therefore individual stratification of both VTE and bleeding risk would seem prudent prior to prophylaxis.

Clinical bottom line

The use of LMWH thromboprophylaxis is effective at reducing the incidence of VTE in ambulatory patients with below-knee plaster casts. For every 14 patients treated, 1 episode of VTE will be prevented. The vast majority of VTE episodes will be asymptomatic DVT. The risk of PE or sudden death without prophylaxis is low

Recommendations

There is evidence to support the use of thromboprophylaxis in ambulatory patients with isolated limb injury who are immobilised in below knee plaster cast. **(Grade A)**

7.4c Patients temporarily immobilised in above knee plaster casts

Three part question

In [patients with lower extremity injury requiring temporary immobilisation with above knee plaster of paris] does [prophylactic anticoagulation with LMWH] reduce the risk of [venous thromboembolic disease within the next three months]?

Search strategy

MEDLINE and EMBASE via the OVID interface the week ending the 8th July 2011. The Cochrane database was also searched using direct terminology.

MEDLINE: (exp venous thrombosis OR exp thromboembolism OR exp pulmonary embolism OR DVT.mp OR depp vein thrombosis.mp OR PE.mp OR pulmonary embolism.mp OR venous thromb\$.mp) AND (exp casts surgical OR plaster cast\$.mp OR exp immobilization OR immobilization.mp)

EMBASE: (exp vein thrombosis OR exp thromboembolism OR exp lung embolism OR exp venous thromboembolism OR exp deep vein thrombosis OR DVT.mp OR deep vein thrombosis.mp OR PE.mp OR pulmonary embolism.mp OR venous thromb\$.mp) AND (exp plaster cast OR exp immobilization OR plaster cast\$.mp OR immobilisation.mp)

All searches were limited to human studies only.

Search outcome

440 and 1280 records were found in the MEDLINE and EMBASE searches respectively. Following an initial abstract review 14 of these were deemed relevant. However, 13 were subsequently rejected as they either duplicated data presented elsewhere (nine) or they did not include patients treated in above knee casts (four).

Comments

The evidence for use of thromboprophylaxis in ambulatory patients immobilised with above knee casts is limited and comes from a single RCT (25). Unfortunately these patients were not part of a pre-determined subgroup and therefore the numbers included are

small and no statistical analysis has been performed. However, the data suggests an ARR in the order of 8% associated with the use of thromboprophylaxis, which would give an NNT of 12. These results are comparable with the effect of thromboprophylaxis seen in patients treated with below knee casts (9). Given that an above knee cast provides a greater degree of immobility (7) it would be logical to assume that the risk of venous thromboembolism is at best the same with the two different types of immobilisation. It should also be noted that a large proportion of above knee casts are also non-weight bearing, which has itself been demonstrated to be an independent risk factor for the development of VTE in ambulatory patients with lower limb immobilisation (43).

Clinical bottom line

Although the evidence examining the use of thromboprophylaxis in this specific subgroup is limited, that which does exist indicates the use of thromboprophylaxis is effective at reducing the incidence of VTE.

Recommendation

Ambulatory patients immobilised in above knee plaster casts are at increased risk of VTE and thromboprophylaxis should be considered. **(Grade C)**

7.5 Thromboprophylaxis

- a. Type
- b. Duration

7.5a Can we use oral thromboprophylaxis for temporary immobilisation in ambulatory patients with isolated limb injury

Three part question

In [ambulatory patients with temporary immobilisation of the lower limb following isolated trauma] does the use of [aspirin, a factor Xa inhibitor or any other method of oral thromboprophylaxis] prevent [venous thromboembolic disease over the subsequent three months]

Search strategy

MEDLINE was searched using the OVID Interface from 1948 to July Week 1 2011. EMBASE was searched using the OVID Interface from 1980 to 2011 Week 27. The Cochrane Database of Systematic Reviews was also searched using direct terms.

[(lower limb adj (immobiliz\$ or immobilis\$)).mp. OR Immobilization/ OR (Immobiliz\$ or Immobilis\$) OR exp Casts, Surgical/ OR plaster cast.mp OR plaster of paris.mp OR exp Splints/] AND [exp Lower Extremity/ OR Lower Extremity.tw OR exp LEG/] AND [Aspirin/ OR aspirin.mp. OR Factor Xa/ OR factor xa inhibitor.mp] AND [exp Thromboembolism/ OR exp Venous Thrombosis OR exp Deep Vein Thrombosis OR thromboembolism.mp OR thrombo\$.mp OR exp Sudden death/ OR pulmonary embolism.mp]

Search outcome

37 papers were found, of which only one addressed the three part question (47).

Comment(s)

Multiple prospective randomised controlled trials have been conducted investigating the use of LMWH as thromboprophylaxis for transiently immobilised patients with limb injury. Unfortunately, little evidence investigates the efficacy of other forms of prophylaxis. The increasing emergence of studies supporting the prophylactic use of oral factor Xa inhibitors in orthopaedic surgery (48, 49) will no doubt lead to wider use of these drugs within thromboembolism research. As yet, they have not been trialled in immobilised ambulatory patients. Only one trial has assessed the use of aspirin in this situation. This was a pilot study in a German Journal with several methodological concerns.

Clinical bottom line

There is currently little evidence to support the use of oral thromboprophylaxis for ambulatory patients with immobilisation of the lower limb. While pilot studies would suggest aspirin may have a similar efficacy to LMWH, further trials are needed. If required, prophylaxis should be currently achieved with LMWH, for which a large evidence base exists.

Recommendation

Current evidence investigating oral anticoagulants is too limited to allow recommendation of any oral therapy as thromboprophylaxis for ambulatory patients with temporary lower limb immobilisation. (**Grade B**)

7.5b If the decision is taken to prescribe thromboprophylaxis for immobilised ambulatory limb trauma, what duration of prophylaxis is indicated?

Three part question

In [ambulatory patients with temporary lower limb immobilisation] what is [the optimum duration of thromboprophylaxis needed] to prevent [a venous thromboembolic event]?

Search strategy

MEDLINE and EMBASE databases were searched via the OVID interface the week ending the 8th April 2012 using the following strategies.

MEDLINE : (exp venous thromboembolism OR exp pulmonary embolism OR exp thromboembolism OR exp venous thrombosis OR venous thromboembolism.mp OR deep vein thrombosis.mp OR DVT.mp OR pulmonary embolism.mp OR PE.mp OR venous thromb\$.mp) AND (Casts, surgical OR plaster cast\$.mp OR plaster of paris.mp OR exp immobilization OR immobilisation.mp) AND (exp heparin OR exp anticoagulants OR exp heparin, low-molecular-weight OR low molecular weight heparin.mp OR thromboprophylaxis.mp)

EMBASE: (exp vein thrombosis OR exp thromboembolism OR exp lung embolism OR exp venous thromboembolism OR exp Deep vein thrombosis OR deep vein thrombosis.mp OR DVT.mp OR pulmonary embolism.mp OR venous thromb\$.mp) AND (exp plaster cast OR plaster cast.mp OR exp immobilization OR immobilisation.mp) AND (exp heparin OR exp low molecular weight heparin OR exp anticoagulant agent OR thromboprophylaxis.mp)

Both searches were limited to human studies only.

Search outcome

The above searches generated 212 and 826 citations respectively. None of these were found to be directly relevant to the three part question.

Comment(s)

There have been no studies examining the optimum duration of thromboprophylaxis needed in ambulatory patients with plaster cast immobilisation. The studies which provide evidence for the use of thromboprophylaxis in this patient cohort universally gave LMWH for the duration of the plaster cast and in the absence of any good evidence to the contrary it would seem prudent to recommend the same (25, 26, 42, 50). A recommendation which is in keeping with the recent NICE guidance and the conclusions from the recent Cochrane review, both of which advise clinicians to offer LMWH for the duration of the plaster cast if indicated (1, 9). However, the risk of having a VTE event is unlikely to remain the same throughout the period of immobilisation. The highest risk of developing a venous thrombosis is maximal during the first 10 days post injury and the risk is likely to lessen as patients are allowed to weight bear towards the end of their treatment. This could be used as an argument for limiting the use of thromboprophylaxis to the period of highest risk, an approach which is in keeping with some (17, 41) but not all (46, 51), clinicians who commonly use prophylaxis in this patient cohort.

Clinical bottom line

There is no good evidence regarding the duration of thromboprophylaxis needed in ambulatory patients with temporary lower limb immobilisation. Therefore, it is the recommendation of the authors that thromboprophylaxis should be continued for the duration of the plaster cast, in line with the recent NICE guidance.

Recommendation

If commenced, prophylactic LMWH should be given for the duration of the plaster immobilisation period. **(Grade E)**

7.6 Risks associated with thromboprophylaxis

What are the risks associated with prescription of thromboprophylactic doses of LMWH over a several week period, with specific reference to HIT/major bleeding.

Three part question

In [patients with lower extremity injury requiring temporary immobilisation] does [prophylactic anticoagulation with LMWH] increase the incidence of [fatal, major or minor bleeding episodes].

Search strategy

MEDLINE and EMBASE databases were searched using the OVID interface the week ending the 8th July 2011 using the following strategies.

MEDLINE: (exp Casts, Surgical OR plaster cast\$.mp OR exp immobilization OR immobilisation\$) AND (exp Heparin, low-molecular-weight OR exp enoxaparin OR exp Dalteparin OR LMWH.mp OR low molecular weight heparin.mp OR clexane.mp OR dalteparin.mp OR fragmin.mp OR tinzaparin.mp OR enoxaparin.mp)

EMBASE:(exp plaster cast OR plaster cast\$.mp OR exp immobilization OR immobilisation.mp) AND (exp low molecular weight heparin OR low molecular weight heparin.mp OR LMWH.mp OR exp enoxaparin OR enoxaparin.mp OR clexane.mp OR exp dalteparin OR dalteparin.mp OR fragmin. mp OR exp tinzaparin OR tinzaparin.mp)

All searches were limited to human studies only

Search outcome

101 and 460 records were found respectively. Four unique randomised controlled trials (RCTs) examining the study population were found, along with one prospective observational review and 2 meta-analyses. The two meta-analyses (9, 44) include the same six papers, four of which are the RCTs identified. Therefore the Cochrane review, along with the prospective observational study (52), is presented below as it gives the most complete data regarding adverse events.

Comment(s)

The use of prophylactic low molecular weight heparin (LMWH), for the prevention of venous thromboembolism (VTE), is widely employed in both the inpatient and outpatient setting. As with all anticoagulant therapy, its use is associated with an increased risk of bleeding and additionally a theoretical risk of heparin induced thrombocytopenia (HIT) is present, although this is less common with low molecular weight than with unfractionated heparin. The evidence presented demonstrates the use of LMWH to be safe in the target population: a risk of major bleeding of 0.11 – 0.27% is reported (9, 44, 52), with a number needed to harm of 769. When this is compared with the estimated number needed to treat of 14 to prevent one VTE event in the same cohort, it follows that the benefits of LMWH prophylaxis outweigh the risks (9). In addition no deaths from bleeding were reported in either of the presented studies as well as minimal rates of minor bleeding (1.51 – 2.7%) and HIT (0 – 0.17%) (9, 51). Furthermore it is worth noting that LMWH thromboprophylaxis has been proven to be equally safe in the elderly (a sub-group which can cause particular concern) with studies demonstrating rates of major bleeding and HIT of 0.4 – 0.49% and 0.54 - 1.4% respectively (53, 54), although it is important to note that these studies have been carried out in medical patients and not the target cohort. As persuasive as these figures regarding the benefits and risks of LMWH thromboprophylaxis are, it is important to consider each patient on an individual basis and it is worth remembering that high risk patients, both for bleeding and VTE risk, have been excluded from the studies likely resulting in an exaggeration of the overall benefit and risk ratio.

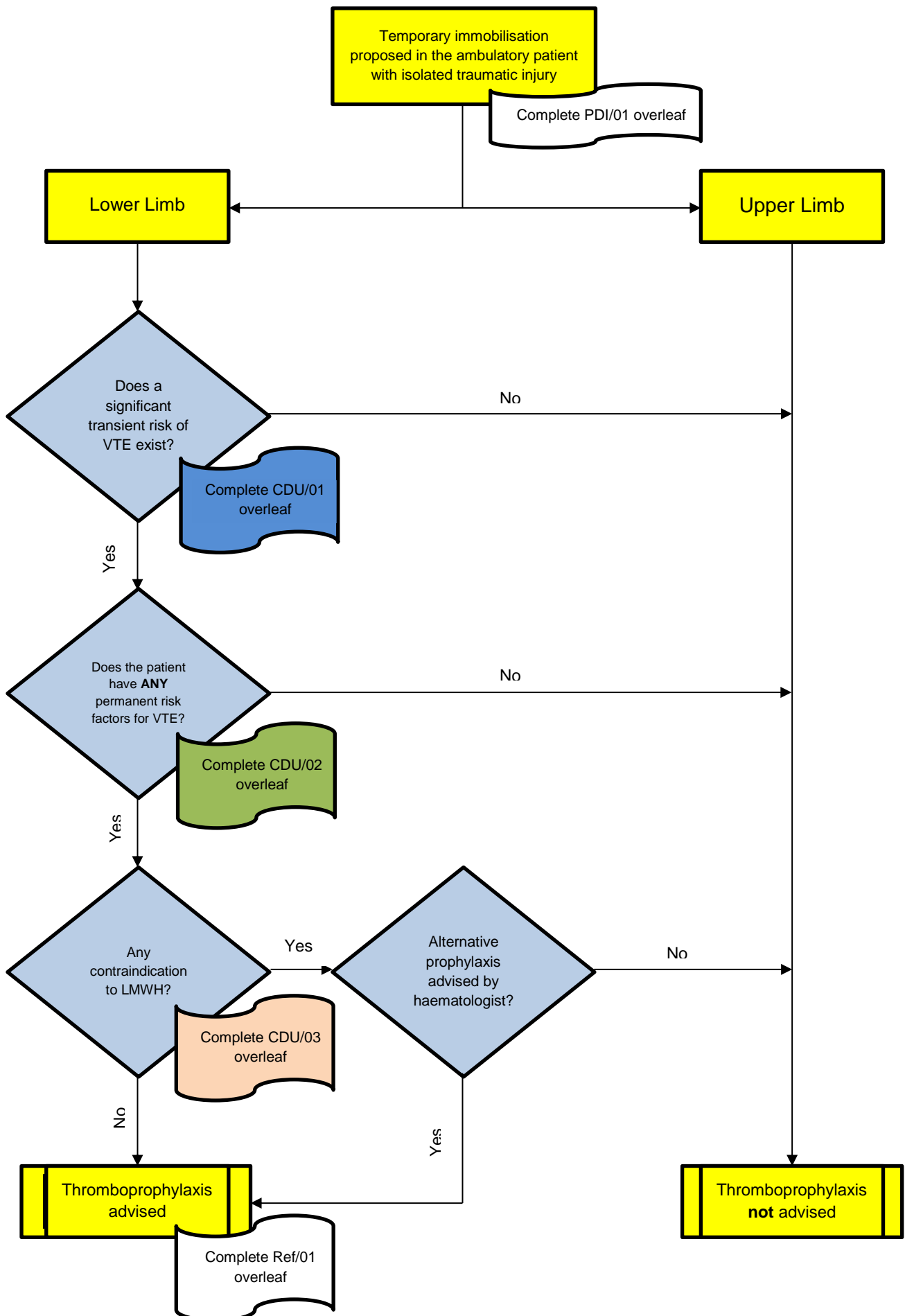
Clinical bottom line

Low molecular weight heparin is safe to use as thromboprophylaxis in patients with lower limb plaster casts. Associated rates of major bleeding and thrombocytopenia are low, less than 0.2% in the related cohort.

Recommendations

The use of prophylactic LMWH is associated with low rates of heparin induced thrombocytopenia and major bleeding when used for thromboprophylaxis in ambulatory patients with plaster cast immobilisation. **(Grade A)**

8. Evidence-based flowchart



PDI/01: SUITABILITY FOR PROTOCOL DRIVEN THERAPY

Isolated traumatic limb injury suitable for ambulatory outpatient care	Yes
Age > 16 years	Yes
Any immobilisation proposed (to include splint, non-weight bearing crutches or any form of plaster cast)	Yes

CDU/01: DOES A TRANSIENT RISK OF VTE EXIST? (ANY YES)

Rigid immobilisation in plaster cast	Yes
Non-weight bearing status	Yes
Acute severe injury (dislocation, fracture or complete tendon rupture)	Yes

CDU/02: DOES ANY PERMANENT RISK OF VTE EXIST? (ANY YES)

Current hormone therapy (COCP, HRT, Tamoxifen)	Yes
Personal or first degree relative VTE history	Yes
Active smoker	Yes
Any recent hospital admission / major surgery	Yes
Pregnant or immediately post-partum	Yes
Any serious medical comorbidity including cardiac failure/COPD/chronic renal failure or inflammatory bowel disease	Yes
Extensive varicosities	Yes
Active cancer	Yes
Obesity (BMI > 30)	Yes
Known thrombophilia	Yes
Age > 60 years	Yes

CDU/03: ANY RELATIVE CONTRAINDICATION TO LMWH? (ANY YES)

Haemophilia / other haemorrhagic disorder	Yes
Thrombocytopenia or previous Heparin induced Thrombocytopenia	Yes
Recent cerebral haemorrhage or severe hypertension	Yes
Active peptic ulcer / recent gastrointestinal bleeding	Yes
Recent major trauma / surgery to eye or nervous system	Yes
Hypersensitivity to any form of heparin	Yes
Known estimated GFR <30ml/min	Yes
Risk deemed to outweigh benefits by clinician	Yes

REF/01: THROMBOPROPHYLAXIS IS ADVISED (ALL YES)

Obtain baseline eGFR and/or platelet count for all patients with suspected or known renal impairment and/or thrombocytopenia	Yes
Any patient with baseline moderate or worse renal impairment (eGFR <50ml/min) to be dose adjusted as per BNF/pharmacist guidance	Yes
Prophylactic dose subcutaneous LMWH once daily prescribed until date of clinical / orthopaedic review	Yes
Patients educated regarding s/c injection technique OR district nurse referral for ongoing injections	Yes
Safety net in place re: bleeding complications	Yes
Written guidance to patient and GP regarding signs of HIT/coagulopathy and advice to consider platelet check in 5 days' time if review delayed.	Yes

Appendix 1 (tables from BETS)

Table 1: Risk in upper limb immobilisation

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
Blom JW, Doggen CJ, Osanto S, Rosendaal FR. November 2005 The Netherlands	179 Patients presenting between March 1999 and September 2003 with a first upper limb DVT. A comprehensive questionnaire was given to each individual in order to identify possible risk factors. This data was compared to that obtained from approx 2400 control subjects	Population-based case-control study (Level of evidence 3b)	Adjusted Odds ratio for upper limb DVT in those with recent plaster cast immobilisation	3/79 vs 7/2398 = 7(95% CI 1.7 to 29.5)	Relatively small number of cases. In addition, the study recruits participants from anticoagulant centres. Finally the study only includes the use of plaster casts as "immobilisation".
Martinelli I, Battaglioli T, Bucciarelli P, Passamonti SM, Mannucci PM. August 2004 Italy	115 Patients presenting for thrombophilia screening after an episode of upper-extremity DVT.	Retrospective cohort study (level of evidence 2b)	No. of individuals with documented upper limb immobilisation prior to an upper limb DVT	0%	The patients were recruited from a centre for thrombophilia screening, perhaps resulting in some bias in the population represented in this study. Also this is a relatively small study (115) involving only one centre.
			Patients with preceding upper limb trauma	4%	
Marinella et al 2000 USA	90 adult patients with Deep Vein Thrombosis (DVT) of the internal jugular, subclavian, axillary, or brachial vein over a 5-year period.	Retrospective observational cohort study in a large urban teaching hospital (level of evidence 2b)	Prevalence of most common underlying risk factors for upper extremity DVT	Central Venous Catheter (CVC) 72%, Infection 28%, Extrathoracic malignancy 22%, and recent surgery 21%	Retrospective study of a small cohort. In addition, as it is a retrospective study, it is difficult to know whether patients had underlying hypercoagulable states e.g. factor V Leiden mutation as most patients were not evaluated for such conditions.
Spencer et al 2007 USA and Canada	483 adult patients with validated acute Deep Vein Thrombosis (DVT), 14% of whom (69 patients) were diagnosed with upper extremity DVT.	Retrospective observational cohort study (Level of evidence 2b)	upper extremity DVT risk factors (%) (n=69)	Central Venous Catheter (CVT) 62.3%, Surgery within the 3 months prior to DVT diagnosis 48.5%, Fracture within 3 months of DVT diagnosis 15.9%	A small sample size. The medical record limits the information available on patient medical history and clinical characteristics

Table 2: Risk in lower limb immobilisation

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
Patil et al 2007 England	100 Ambulatory patients immobilised in lower limb cast for conservatively treated ankle fractures	Prospective observational cohort (level of evidence 2b)	Incidence of DVT on cast removal	5/100 = 5% (95% CI 1 to 9%)	72% patients were fully weight bearing within the plaster. Duration of time in cast ranged from 3 to 7 weeks.
Testroote et al 2008 Netherlands	388 ambulatory non-surgical patients in temporary immobilisation following isolated lower limb injury	Prespecified subgroup analysis within systematic review (level of evidence 2a)	Incidence of deep vein thrombosis in conservatively treated patients	44/388 = 11.3% (no confidence intervals provided)	Included studies which excluded those patients at high risk of VTE - likely underestimating incidence. No distinction made between proximal/distal and symptomatic/asymptomatic DVT.
Nilsson-Helander et	100 consecutive patients with acute	Prospective observational cohort	Colour duplex sonography	32/95 = 33.7%	Small numbers. Underpowered. Initial thromboprophylaxis for

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
al 2009 Sweden	achilles tendon rupture, of which half were randomised to conservative non-surgical treatment	(level of evidence 2b)	verified thrombosis in all patients Colour duplex sonography verified thrombosis in non surgical patients PIOPED verified pulmonary embolism in non surgical patients	18/46 = 39.1% 3/46 = 6.5%	operative patients and then based on surgical preference.
Healey et al 2010 New Zealand	208 patients with an injury to the tendo achilles requiring immobilisation in a cast, treated for >1/52 as an outpatient.	Retrospective audit to identify patients with achilles injury, followed by cross reference with VTE database and retrospective medical record review to identify VTE events.	Cumulative symptomatic VTE events within the cohort Confirmed Pulmonary Embolism within the study period Proximal DVT within the study period Distal DVT within the study period	6.3% (95% CI 3.4 to 10.5) 1.4% 1.9% 2.9%	Patients with follow up outside district excluded. 20% cohort underwent some form of surgical intervention throughout the study period.

Table 3: Individualised Risk Assessment

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
Riou et al 2007 France	3698 adult patients presenting to the ED with isolated non surgical lower limb injury below the knee. 2761 (75%) completed follow up and underwent full leg compression ultrasound of the affected limb.	Prospective multicentre observational cohort (level of evidence 2b)	Incidence of VTE after removal of immobilisation Predictive Variables of VTE development after multivariate analysis	6.4% (95% CI 5.5 to 7.4%) Age >50 (OR 3.14, p<0.0001), Rigid immobilisation (OR 2.70, p<0.0001), Non weight bearing status (OR 4.11, P=0.0015) and Severe injury (OR 1.88, p=0.0002)	ED physicians were left to decide on type of VTE prophylaxis: over 60% patients received some form of pharmacological prophylaxis. This sample is thus not truly reflective of an untreated Emergency Department population. Only 75% ultrasound follow up rate (2761 patients).
Eisele et al 1998 Germany	731 outpatients with recent injury or surgery of the leg/pelvis. All patients underwent pre and post ultrasonic investigation for DVT in the lower extremities.	Prospective interventional cohort. A subjective scoring system to ascertain risk of VTE within the cohort was created based on previous research and expert opinion. This scoring system was applied to each patient with a binary risk outcome and prescription of prophylaxis in tandem with a 'high risk' score. (level of evidence 4)	Incidence of VTE in patients deemed to be at 'high risk' of development. Incidence of VTE in patients deemed to be at 'low risk' of development.	4% 0.6%	Scoring system was not independently derived from original research (no mention of risk stratification/risk ratios for independent variables/derivation set). All patients deemed to be at high risk were treated with LMWH/UFH. No attempt at external validation. No confidence intervals given. No sub group analysis to identify risk factors for those developing DVT in the conservatively treated cohort.
Kujath et al	253 ambulatory	Prospective	Incidence of	4.8%	No multivariate analysis

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
1993 Germany	outpatients with lower limb injuries treated with immobilisation by plaster cast	randomised controlled trial. 126 patients randomised to LMWH and 127 receiving no thromboembolic prophylaxis. Data on risk factors collated and analysed to determine quantifiable risk in relation to development of thrombosis. (level of evidence 2b)	VTE in therapeutic arm Incidence of VTE in conservative arm Number of average risk factors present in patients developing DVT	16.5% 1.96	performed on individual risk factors: the presence of each risk factor was compared in patients with and without thrombosis to evaluate statistical significance. Included patients undergoing surgical intervention at a later date. 5 patients had DVT on ultrasound with failed phlebographic confirmation.
Giannadakis et al, 2000, Germany	178 ambulatory patients immobilised in plaster casts for lower limb injuries deemed to be at low risk of thromboembolic disease, and therefore prescribed no pharmacological prophylaxis. Most of these patients had a fibular ligament injury (144), with the remaining 34 patients having metatarsal fractures (16), ankle fractures (11), calcaneal fractures (4) and talar fractures (3).	Prospective observational cohort. All patients were clinically examined and underwent colour-coded duplex sonography for detection of DVT after removal of the cast at the end of the immobilisation period. Confirmation of DVT was performed by contrast venography when suspected on ultrasound (level 2b)	Incidence of lower limb DVT within the cohort Incidence of clinically suspected pulmonary VTE within the cohort	1.1% (95% CI 0% to 4.4%) 0%	Very low incidence of fractures within the cohort and no subgroup analysis. 'Low risk' cohort defined by local guidance rather than validated decision tool. Investigation of pulmonary VTE based on clinical suspicion only. Limited data on method of duplex assessment including objective criteria for diagnosis of calf thrombi.

Table 4: Splints

No Papers

Table 5: Below knee immobilisation

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
Testroote M et al 2009 Netherlands	Adult outpatients with lower-limb injuries treated in a brace or plaster cast.	Systematic review and meta-analysis of 6 RCTS (1490 patients). Subgroup analyses included 788 patients managed non-surgically and 894 patients treated in a below-knee cast. (level of evidence 1-)	Overall incidence of DVT Incidence of DVT in conservatively managed patients Incidence of DVT in patients in a below-knee POP	Placebo group: 18.1%, LMWH group: 10% OR 0.49 (95% CI 0.34 - 0.72) Placebo group: 11.3%, LMWH group: 4.2% OR 0.35 (95% CI 0.19 - 0.62) Placebo group 18.6%, LMWH group: 11.8% OR 0.54 (95% CI 0.37 - 0.8)	Statistical and clinical heterogeneity. The number of patients in the included studies are small. The assessment of patients in below-knee plaster casts includes patients managed surgically.

Table 6: Above knee immobilisation

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
Kock H-J et al 1995 Germany	Ambulatory patients between 18-65 years with leg injuries requiring conservative out-patient management in below-knee or cylinder casts.	Open randomised controlled trial including completed data on 339 patients. 48 were managed in above knee cylinder casts. Patients randomised to receive either no thromboprophylaxis or 32mg of Mono-Embolex. Trial was stopped early due to meeting efficacy criteria. (level of evidence 2b)	Overall DVT rate DVT rate in above knee casts	LMWH group: 0%, Control group: 4.3% p<0.007 LMWH group: 0/24 = 0%, Control group: 2/24 = 8.3% (no statistical analysis)	Open study with no use of placebo. Some high risk groups (previous DVT and pregnancy) excluded. High post recruitment exclusion (52 patients) although intention to treat analysis performed. Only small numbers of patients with above knee casts included and no statistical analysis performed.

Table 7: Type of thromboprophylaxis

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
Gehling et al. January 1998 Germany	287 patients presenting with lower extremity injuries, who required immobilising bandages or casts.	Randomized controlled trial in which thromboprophylaxis was administered in the form of a subcutaneous injection of divarin 1750 once daily in 143 patients and with Aspirin 2 x 500 mg orally in 144 patients. A clinical examination and colour-coded duplex sonography were performed after removal of the cast for detection of lower extremity venous thrombosis. A phlebography was performed for confirmation when thrombosis was suspected.	Incidence of DVT in group receiving prophylactic LMWH Incidence of DVT in group receiving prophylactic Aspirin	9/143 (6.3%) 7/144 (4.8%)	Heterogenous cohort consisting of inpatients, outpatients and surgical patients. No distinction between symptomatic/asymptomatic disease

Table 8: Risks of thromboprophylaxis

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
Testroote M et al 2008 Netherlands	Patients with lower limb injuries managed as outpatients in lower limb plaster casts or braces.	Six studies included (1490 patients) of which 4 studies included patients treated non-surgically (788 patients). 750 patients were given thromboprophylaxis with LMWH. (level of evidence 1a)	Incidence of major bleeding Incidence of minor bleeding	LMWH group: 2 patients (0.26%), Control group: 1 patient (0.14%) LMWH group: 14 patients (1.87%), Control group: 12 patients (1.62%)	Statistical and clinical heterogeneity. The numbers of patients included in the studies are small. The assessment of safety includes patients managed surgically. One of the studies included uses as a sub-prophylactic dose of LMWH.
Otero-Fernandez R	Orthopaedic patients requiring out-patient	Prospective uncontrolled multicenter cohort (Level	Incidence of major Bleeding	Overall: 0.17%,	No control group. Two different doses of

et al 2008 Spain (157 centres)	thromboprophylaxis with Bemiparin. Included 6456 patients, of which 1789 patients were managed conservatively with cast immobilisation.	of evidence 2b)		Plaster- cast group: 0.11%	Bemiparin used (2500IU and 3500IU) selected at clinicians discretion.
			Incidence of minor Bleeding	Overall: 4.57%, Plaster- cast group: 1.51%	
			Incidence of Thrombocytopenia	Overall: 0.51%, Plaster- cast group: 0.17%	

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