



Venous Thromboprophylaxis in Critical Care

STANDARDS AND GUIDELINES

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Abbreviations used in this document

DVT	Deep vein thrombosis
GECS	Graduated elastic compression stocking
HCW	Health care worker
HIT	Heparin induced thrombocytopenia
ICU	Intensive care unit
IVCF	Inferior vena-caval filter
LMWH	Low molecular weight heparin
PE	Pulmonary embolism
UFH	Unfractionated heparin
VTE	Venous thromboembolic disease

1. Summary

The purpose of this document is to draw together the current evidence base relating to thromboprophylaxis in the critically ill and suggest guidelines which reflect current best practice. The aim is to reduce both the incidence and the severity of thrombotic events in patients in both medical and surgical intensive care units.

Recommendations will be discussed, critiqued and graded according to the following system.

Table 1. Grading Scheme

Grading of Recommendations

- A. Supported by at least two level I investigations
- B. Supported by one level I investigation
- C. Supported by level II investigations only
- D. Supported by at least one level III investigation
- E. Supported by level IV or V evidence

Grading of evidence

- I. Large randomised control trials with clear-cut results; low risk of false positive error or false-negative error
 - II. Small, randomised trials with uncertain results; moderate to high risk of false-positive and/or false negative results.
 - III. Nonrandomised, contemporaneous controls
 - IV. Nonrandomised, historical controls and expert opinion
 - V. Case studies, uncontrolled studies and expert opinion
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2. Introduction

The critically ill represent a specific population of patients who are at substantially increased risk of venous thromboembolism (VTE) which contributes significantly to their morbidity and mortality [1-3]. Pulmonary embolism (PE) is frequently seen at post mortem in these patients, the incidence being as high as 27% [3-5]. The incidence of image-proven deep venous thrombosis (DVT) in critically ill patients ranges from <10% to almost 100% depending upon the screening methods and diagnostic criteria used.

Most critically ill patients have multiple risk factors for VTE. Many risk factors pre date intensive care unit (ICU) admission such as recent surgery, trauma, sepsis, malignancy, immobilisation, increased age, heart or respiratory failure and previous VTE. These initial VTE risk factors are confounded by others, which, are acquired on the ICU including immobilisation, pharmacologic paralysis, central venous catheterisation, additional surgical procedures, sepsis, vasopressors and haemodialysis [6]. The relative importance of each of these factors and their individual and cumulative effect on the risk of VTE is unknown.

Clinically undetected DVT may well be present prior to admission to the ICU. Five studies looking at a total of 990 patients (using Doppler ultrasound) reported a rate of 5.5% DVT on admission to ICU with rates up to 29% in patients not given thromboprophylaxis prior to ICU admission [7-11]. Although the majority of DVTs are clinically silent and often confined to the calf veins, asymptomatic DVT can become symptomatic and lead to embolic complications [12]. There is no way of predicting which at-risk patients will develop symptomatic VTE and massive pulmonary embolism (PE) frequently occurs without warning and is often fatal [12]. Although this may represent an overestimate, the prevalence of PE at autopsy in hospital inpatients has been to be found to be 15% [13].

Hospitalised patients recovering from major trauma have the highest risk of developing VTE. Without adequate thromboprophylaxis patients with multi-

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system failure or major trauma have a DVT risk exceeding 50%, with PE being the third leading cause of mortality after the first day [6].

There are extensive trials of thromboprophylaxis for medical and surgical patients [6,14] but far fewer for critical care patients. Extrapolating data relating to specific medical and surgical patients to the critically ill is not easy as the risk benefit ratio is significantly different between these groups [3].

3. Screening for Thrombosis on ICU

Recommendation

- **Thromboprophylaxis should be reviewed daily in all ICU patients. Grade E**
- **Although Doppler ultrasound is used to diagnose clinically suspected DVT, its routine use for screening in all patients admitted to critical care units cannot be recommended. Grade E**

Rationale:

Although the incidence of asymptomatic DVT on admission to ICU may be as high as 5.5%, history and physical examination are not useful in identifying its presence as 80% of DVT are clinically undetectable [17]. Patients may have transient contraindications (e.g. thrombocytopenia, surgical procedure) to thromboprophylaxis and an individual's risk/benefit ratio may change on a daily basis. Taking this into consideration it is reasonable to propose that thromboprophylaxis be reviewed daily to try to minimise any potential delay in starting appropriate therapy.

In a group of critically ill patients who did not receive thromboprophylaxis but underwent ultrasound detection rates of DVT ranged between 13% and 31% [7,9-11]. A recent study after hip and knee replacement showed that ultrasound only detected 30% of DVT compared to venography [18]. There is a substantial potential for screening to miss a VTE; and no data to suggest that routine ultrasound screening for DVT instead of thromboprophylaxis, is either clinically effective or cost effective in the critically ill.

4.1 Mechanical measures of thromboprophylaxis

Recommendation

- **When pharmacological thromboprophylaxis is contraindicated mechanical thromboprophylaxis should be used. Grade A**
- **In patients at very high risk of thrombosis mechanical thromboprophylaxis can be employed in conjunction with pharmacological therapy. Grade E**

Rationale:

Immobility increases the risk of DVT tenfold [19-21]. Mechanical methods of thromboprophylaxis act by reducing venous stasis in the leg. The major advantage of these methods is the avoidance of systemic anticoagulation and the incumbent risk of bleeding. Calf compression techniques are relatively free of significant side-effects. The options include graduated elastic compression stockings (GECS), (either thigh or calf length) and intermittent pneumatic compression devices. Both methods have been trialled in the critical care population. A recent review by Limpus examined a total of 21 studies relating to the use of mechanical thromboprophylaxis in the critically ill [20]. The meta-analysis of two randomised controlled trials with similar populations showed that neither GECS nor compression devices led to a significant reduction in the risk of thromboembolism [22]. In addition, no trial of mechanical thromboprophylaxis has been shown to reduce the risk of death due to PE [6]. The inherent nature of the intervention makes it almost impossible to blind studies and this compromises the research involved.

It is reasonable to consider that mechanical devices may act in a synergistic manner when combined with pharmacological thromboprophylaxis. A large systematic review of by the Health Technology Assessment Group showed that the use of mechanical compression after surgery reduces the risk of DVT by about two thirds when used as dual therapy and by about half as monotherapy [23]. However, this assumption has not been confirmed in a critical care population.

4.2 Contraindications to mechanical thromboprophylaxis

Mechanical methods of thromboprophylaxis are contraindicated in patients with critical limb ischemia, limb fractures, severe neuropathy and cellulitis of the lower limb. If a patient has been admitted and not received thromboprophylaxis for greater than 72 hours their use is relatively contraindicated because of the theoretical risk of embolisation of a thrombus when the pneumatic pressure is applied. A small proportion of patients find these devices uncomfortable and are unable to tolerate them.

4.3 Graduated elastic compression stockings (GECS)

GECS reduce venous stasis by applying a graded degree of compression to the ankle and calf, with greater pressure being applied distally. They have been shown to reduce the incidence of postoperative venous thrombosis only in low risk general surgical patients and in selected moderate risk patients e.g., neurosurgical. There are no good trials as yet in medical patients. As with pneumatic compression devices stockings cannot be applied if there has been trauma to the lower limbs and their use is also contraindicated in the presence of severe peripheral vascular disease.

5.1 Pharmacological methods of thromboprophylaxis

Studies are limited on the use of pharmacological agents for thromboprophylaxis in the ICU. The agents available for use include aspirin, unfractionated heparin (UFH), low molecular weight heparins (LMWH), fondaparinux and warfarin.

5.2 Aspirin

Recommendation

- **Aspirin should not be used as thromboprophylaxis in the critical care unit. Grade A**

Rationale:

The antiplatelet effect of aspirin and its importance in the primary and secondary prevention of atherosclerotic disease is well established. Its role in venous thromboprophylaxis is based on methodologically flawed studies [22,23], and it has been shown to increase bleeding risk. Aspirin provides less effective thromboprophylaxis than LMWH; aspirin reduces risk of DVT by less than 30% whereas LMWH reduces the risk by 60-70%.

Critically ill patients are more likely to suffer the deleterious consequences of aspirin therapy, including increased risk of haemorrhage and reduced urinary prostaglandin synthesis decreases glomerular filtration. As other agents have been demonstrated to be more efficacious and have a better safety profile when used as thromboprophylaxis in medical and surgical patients, the use of aspirin as thromboprophylaxis in the critical care population cannot be recommended.

5.3 Unfractionated Heparin (UFH)

Recommendations

- **Subcutaneous low dose unfractionated heparin is effective for thromboprophylaxis in the critically ill but its efficacy and safety profiles suggest it should only be used when LMWHs are contraindicated. Grade C**
- **When using unfractionated heparin a dose of 5000 units subcutaneously 8 hourly is preferred to 5000 units twice daily. Grade E**
- **Low molecular weight and subcutaneous unfractionated heparin are contra-indicated in patients with heparin-induced thrombocytopenia in the last six months. Grade A**

The 1975 International Multicenter trial of low-dose UFH thromboprophylaxis reduced the risk of DVT and fatal PE in surgical patients [24]. Subsequent meta-analysis of 74 trials demonstrated that low-dose UFH reduced the rate of post-operative DVT, PE and fatal PE by 67%, 47% and 64% respectively [25]. There are fewer trials relating to UFH in medical patients but meta-analysis of the use of heparin in this cohort has shown significant reductions in the risk of both fatal and non-fatal PE and a non-significant reduction in the risk of DVT [26, 27].

There have been three randomised clinical trials comparing UFH to placebo in critical care patients. In the first, 119 general ICU patients received either UFH 5,000 BD or placebo [28]. The DVT rates by radio-labelled fibrinogen scanning in the UFH arm were 13% compared to 29% in the control arm, a relative risk reduction of 55% ($p < 0.05$). The same group compared sodium and calcium heparin against placebo in 234 patients and found positive leg scans in 19% of controls, 12% after sodium heparin and 8% after calcium heparin. Calcium heparin was associated with significantly more local haematomas and pain [29]. Kapoor et al studied 791 patients; DVT was detected in 31% of the placebo treated group but only 11% of the UFH group

(RRR 65%, $p=0.001$); PE was reduced from 5% to 2% in the treated group [30].

UFH has an inferior safety profile when compared to LMWH for it has a tenfold increased incidence of fatal heparin induced thrombocytopenia (HIT) when compared to LMWH. After HIT, no heparin should be used until the immune response has settled. In an emergency heparin could be used again after 6 months, but an alternative anticoagulant is preferable as HIT is likely to recur [31]. With long term use such as in pregnancy there is a 2% risk of osteoporotic fracture with UFH [32,33]. There has been one study comparing UFH to LMWH in 325 medical ICU patients. DVT was detected by ultrasound in 16% of patients receiving UFH compared to 13% on LMWH, with no differences noted in the rates of proximal DVT or bleeding [34].

5.4 Low molecular weight heparin

Recommendation

- **Thromboprophylaxis with a LMWH is indicated in all patients admitted to an ICU, unless there is a specific contraindication. Grade A**
- **Routine monitoring of factor Xa levels is not warranted in those patients receiving thromboprophylaxis. Grade E**

Rationale:

Fraisse et al. randomised 223 patients receiving mechanical ventilation for exacerbations of COPD to receive nandoparin or placebo [11]. DVT was detected by routine venography in 28% of the placebo group and 15% of those treated with nandoparin, a relative risk reduction of 45% ($p=0.045\%$). There was no significant difference in the major bleeding between the two groups. Similar to other studies in ICU it emphasises that the rate of asymptomatic DVT is high (15%) even in the group receiving thromboprophylaxis.

In medical patients the large MEDENOX trial (enoxaparin) [36] and the PREVENT (dalteparin) study [37] have shown significant risk reduction of VTE in medical in-patients. In PREVENT the incidence of VTE was reduced from 4.96% in the placebo group to 2.77% in the treatment group ($P < 0.001$). The incidence of bleeding was non-significantly higher in the dalteparin group (9 patients; 0.49%) compared to the placebo group (3 patients; 0.16%).

A major limitation of LMWH in the critical care population is the risk of accumulation in patients with renal impairment leading to an unpredictable and excessive anticoagulation. This limits the role of LMWH as thromboprophylaxis in intensive care.

There is some concern that the use of vasopressors may reduce the effectiveness of pharmacological prophylaxis. Critically ill patients receiving vasopressor support had significantly lower anti-Xa levels than those patients not on vasopressors. The putative mechanism is decreased absorption of LMWH from the subcutaneous tissues due to reduced perfusion caused by the vasopressor.

5.5 Warfarin

Recommendation

- **Warfarin is not used for thromboprophylaxis in critically ill patients. Grade E**

Rationale:

Adjusted dose oral anticoagulant therapy with a target INR is not routinely used in the critically ill in the UK. This is because dosing is difficult and unpredictable with a significant risk of both over and under anticoagulation. We are not aware of any trials of warfarin thromboprophylaxis in a critical care setting.

5.6 Fondaparinux

Recommendation

- **Fondaparinux can be used as an alternative measure of thromboprophylaxis in a critical care population, and could be used where heparins are contraindicated such as previous HIT. There is no evidence comparing fondaparinux to LMWH thromboprophylaxis in the critically ill. Therefore it cannot be recommended as routine thromboprophylaxis. Grade E**

Fondaparinux is a new type of anticoagulant, a synthetic anti-Xa agent. It is a synthetic form of the pentasaccharide sequence in heparin that potentiates antithrombin. It binds to antithrombin causing a conformation change in the antithrombin molecule, which, dramatically increases its ability to inactivate factor Xa. A particular benefit of fondaparinux is that it does not cause HIT [38].

Fondaparinux is given as a daily dose of 2.5mg as it has a half-life of 17-18hrs. Prophylactic doses do not prolong the APTT although higher treatment doses may lead to a partial prolongation [39]. Like LMWH, fondaparinux is predominantly excreted renally, thus accumulation occurs in renal failure. Fondaparinux now has a license for use in medical, surgical and orthopaedic thromboprophylaxis and in acute coronary syndrome.

A meta analysis of 4 randomised control trials where fondaparinux was compared to enoxaparin after orthopaedic surgery showed that fondaparinux was more effective at preventing VTE compared to enoxaparin by day 11 (6.8 versus 13.7%). However, there was significantly more major bleeding episodes in those receiving fondaparinux (2.7 versus 1.7; $p=0.008$) [40].

No studies have been undertaken using fondaparinux in a critical care population although a study in 849 older acute medical patients versus placebo showed that it is effective in this group and there was no increased bleeding when compared to placebo [41].

5.7 Contraindications to pharmacological thromboprophylaxis

Many critically ill patients have increased risk of bleeding and therefore pharmacological thromboprophylaxis may be relatively or absolutely contraindicated. Due to the risk of HIT with heparin we recommend that patients receiving unfractionated heparin or LWM heparin, patients should have regular full blood counts to ensure they are not becoming thrombocytopenic.

We recommend against thromboprophylaxis in those with

- **Thrombocytopenia with a platelet count $< 50 \times 10^9/l$**
- **Underlying coagulopathy, such as disseminated intravascular coagulation. We do not give thromboprophylaxis when the INR, or APTT are greater than 1.5.**
- **Evidence of active bleeding**
- **Known bleeding disorder**
- **Lumbar puncture/epidural/spinal analgesia within the previous 4 hours**
- **New ischaemic or haemorrhagic CVA – we wait for two weeks after a thrombotic stroke, and one week after an embolic stroke.**
- **Haemophilia A or B, or severe von Willebrand disease**

These contraindications are empirical and understandably have not been challenged in clinical trials. Therefore we have not assigned a grade of evidence to them.

On a practical level we recommend delaying giving thromboprophylaxis on our unit until 6pm each day. This is based on the assumption that most procedures (e.g. line changes and routine tracheostomies etc) will be performed during standard working hours. Therefore by changing the time at which thromboprophylaxis is given reduces the chances of patients

accidentally missing a dose because they are undergoing a procedure. Theoretically delaying the dose may reduce the chances of bleeding complications.

6. Inferior vena caval filters

Recommendations:

- **Inferior vena cava filters are indicated to prevent pulmonary embolism in patients with deep vein thrombosis who have a contraindication to anticoagulation. Grade B**
- **Routine pharmacological thromboprophylaxis should be started in patients with an inferior vena caval filter as soon as the contraindication to anticoagulation has passed. Grade A**

In some parts of the world prophylactic inferior vena caval filters (IVCF) have been recommended for use in trauma patients. However, there are no studies to support this practice. Indeed recent meta-analyses of prospective studies found no difference in the rates of PE among patients with and without prophylactic IVCs [42]. The primary indication for IVCF is for the prevention of PE in patients with DVT who have a contraindication to anticoagulation [43].

Temporary IVCF may be used in those patients who are at high risk of PE and in whom surgery is planned in the immediate future. The British Society of Haematology guidelines recommend that anticoagulation be considered in all patients with an IVCF once a temporary contraindication to anticoagulation has passed and that IVCF insertion is not indicated in unselected patients with VTE who will receive standard anticoagulant therapy [43].

Decousus et al 1998 studied a mixed population of surgical and medical patients who had a proven DVT and underwent randomisation with regards to insertion of an IVCF [44]. Both groups were anticoagulated with either heparin or low molecular weight heparin. Patients with a contraindication to anticoagulation were excluded from the study. At 12 days 1.1% of the patients with an IVCF had suffered a PE compared to 4.8% in the group without a

filter. After two years follow up however 20.8% of the filter group and 21% of patients in the non-filter group had gone on to suffer further PE [44].

Rosenthal et al (2004) reported the follow up of 94 trauma patients admitted to the ICU who underwent IVCF insertion at the bedside in ICU who were not anticoagulated [45]. Nineteen patients died of their injuries but no deaths were related to IVCF insertion. Filter related complications included 2 groin haematomas and 3 filters misplaced in the right ventricle. Thirty-one patients underwent uneventful retrieval of the IVCF, 44 filters were not removed because either the severity of the trauma prevented pharmacological prophylaxis and in 3 cases because thrombus became trapped in the filter. Long-term follow up was not reported. The authors do not comment on the rate of PE in either group, but conclude that IVCFs can provide a safe bridge to anticoagulation [44, 45].

IVCF use is associated with both short and long term complications. PEs still occur in patients and there may be a tendency to delay anticoagulation when a filter is present. There is also a risk of thrombosis at the site of filter insertion. Where possible and whenever the contraindication to anticoagulation is transient, a retrievable filter should be favoured and anticoagulation commenced when it is no longer contraindicated.

7. Duration of thromboprophylaxis post in-patient discharge

Recommendation

- **Patients after total hip replacement and cancer surgery should be considered for extended thromboprophylaxis post discharge to ensure patients receive 28-35 days of thromboprophylaxis post surgery. Grade A**

Rationale:

VTE causes 60,000 deaths a year in the UK [49], half of which are due hospital admission, therefore it is essential that thromboprophylaxis is continued once these patients are discharged from the ICU. In surgical patients who have undergone total hip replacement or cancer surgery, extended duration thromboprophylaxis has been shown to be beneficial [46, 47]. Such trials have shown that thromboprophylaxis given for 28-35 days post surgery, usually after 4-6 days admission, i.e. 3-4 weeks at home, significantly reduce the risk of VTE when compared to standard use of LMWH. It appears reasonable that critical care patients who fall into this group should be considered for extended prophylaxis, provided there is no increased bleeding risk. No clinical trials have assessed the benefits of extended duration prophylaxis in a mixed ICU population. A large trial of the use of extended thromboprophylaxis has been conducted in medical patients and we are currently awaiting the results [48].

8. Implementation of thromboprophylaxis in critical care

Given the weight of evidence in favour of thromboprophylaxis it is recommended that every critically ill patient should be considered for thromboprophylaxis on admission. There are two risk assessment models; 'opt in' - where all patients are individually assessed and risk scored for their need for thromboprophylaxis, and 'opt out'. 'Opt out' makes the assumption that each patient requires thromboprophylaxis unless there is a contraindication. Due to the high prevalence of VTE in critical care, we recommend the second model.

Some units have introduced a system where LMWH is formally printed up in their drug charts to remind health professionals of the need to prescribe it, with a requirement for it to be crossed out in those patients in whom it is contra-indicated. Similarly TED stockings should be provided for patients at high risk where there is no contraindication.

Compliance with thromboprophylaxis should form part of a continuous ongoing audit with regular feedback and education to ICU staff. It is suggested that at the time of discharge from ICU a specific plan should be documented in the patient's notes with regards to ongoing thromboprophylaxis.

9. Future directions

A 2005 Health Select committee on “The prevention of VTE in hospitalised in-patients” criticised the Department of Health for its failure to fully implement thromboprophylaxis with take up rates of only 30-40% in orthopaedic surgery [50]. In reply the Department of Health set up an Expert Group on VTE who reported in April 2007 [51] and recommended that thromboprophylaxis was made mandatory and embedded in the Clinical Negligence scheme. Currently the “VTE implementation group” are looking at this on behalf of the Chief Medical Officer and are due to produce a national risk assessment tool, which will be audited by the Healthcare Commission in 2009. This will coincide with the publication of NICE guidelines for thromboprophylaxis in all hospitalised in-patients, including critical care in 2009

In the next five years several new anticoagulants, both oral and injectable, short and long acting, are likely to be licensed. Indeed on the last day of writing this document, dabigatran obtained its European license for thromboprophylaxis after orthopaedic surgery. Whether LMWH will survive as the gold standard thromboprophylactic agent is unknown.

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http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleaqueletters/DH_073957

- We would welcome comments on this document and suggestions for other standards in intensive care.
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- Implementation date: September 2008
- Review date: September 2010