# 20 People admitted to critical care units

## 20.1 Introduction

Patients admitted to a critical care facility (who are generally in need of level 2 or level 3 care) can be separated into some distinct groups by their disease process:

- patients with any acute illness that has resulted in one or more organ systems failing and have a need for interventions to support organ function
- patients who need a higher level of observation and intervention that cannot safely be provided elsewhere
- patients who have had complex or prolonged surgical procedures and hence require a duration of recovery with a higher level of observation and monitoring than can be provided elsewhere in order to rapidly detect and mange any deterioration
- patients who are dying and there is ongoing consideration of organ donation.

Each group has its own unique risk factors for VTE and risks of bleeding or other complications. The unifying feature is that during times of severe physiological upset, the inflammatory response is at a maximum and the patient is almost always immobile and likely to have a number of intravascular catheter devices. This puts the patient at a much higher risk of developing venous thrombi. The same patient may however also be at an increased risk of bleeding, either due to a coagulopathy as a consequence of their disease or interventions; or be at risk of bleeding into a surgical field with disastrous consequences such as in spinal surgery or neurosurgery. The medications and equipment used in critical care may increase the risk of bleeding further.

Critically ill patients will have a number of such risk factors which may change in nature, number and significance many times throughout their stay. Also, many invasive procedures may be carried out during such an admission (central lines, lumbar punctures, chest drains etc) and so relative risks of bleeding as a consequence will also change many times.

## 20.2 Review question: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people admitted to critical care units?

For full details see review protocol in appendix C.

**Table 117: PICO characteristics of review question**

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|---|---|
| **Population** | Adults and young people (16 years and older) admitted to critical care units |
| **Interventions** | Mechanical:<br>• Anti-embolism stockings (AES) (above or below knee)<br>• Intermittent pneumatic compression (IPCD) devices (full leg or below knee)<br>• Foot pumps or foot impulse devices (FID)<br>• Electrical stimulation (including Geko devices)<br>• Continuous passive motion<br>• Vena caval filters<br><br>Pharmacological:<br>• Unfractionated heparin (UFH) (low dose, administered subcutaneously) |

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| | • Low molecular weight heparin (LMWH), licensed in UK:<br>○ enoxaparin (standard prophylactic dose 40mg daily; minimum 20mg daily* to maximum 60mg twice daily*)<br>○ dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*)<br>○ tinzaparin (standard prophylactic dose 3500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*)<br>• LMWH, licensed in countries other than UK:<br>○ Bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)<br>○ Certoparin (3000 units daily)<br>○ Nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)<br>○ Parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)<br>○ Reviparin (minimum 1750 units once daily to maximum 4200 units once daily)<br>• Vitamin K Antagonists:<br>○ warfarin (variable dose only)<br>○ acenocoumarol (all doses)<br>○ phenindione (all doses)<br>• Fondaparinux (all doses)*<br>• Apixaban (all doses)*<br>• Dabigatran (all doses)*<br>• Rivaroxaban (all doses)*<br>• Aspirin (up to 300mg)*<br><br>*off-label |
| **Comparisons** | Compared to:<br>• Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only)<br>• No VTE prophylaxis treatment (no treatment, usual care, placebo)<br><br>Within intervention (including same drug) comparisons, including:<br>• Above versus below knee stockings<br>• Full leg versus below knee IPC devices<br>• Standard versus extended duration prophylaxis<br>• Low versus high dose for LMWH<br>• Preoperative versus post-operative initiation of LMWH |
| **Outcomes** | Critical outcomes:<br>• All-cause mortality (up to 90 days after leaving ICU)<br>• Deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days after leaving ICU). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool)<br>• Pulmonary embolism (up to 90 days after leaving ICU). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE<br>• Major bleeding (up to 45 days after leaving ICU). A major bleeding event meets one |

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| | or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding<br>• Fatal PE (up to 90 days after leaving ICU). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE<br><br>Important outcomes:<br>• Clinically relevant non-major bleeding (up to 45 days after leaving ICU): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy.<br>• Health-related quality of life (validated scores only)(up to 90 after leaving ICU)<br>• Heparin-induced thrombocytopenia (HIT) (duration of study)<br>• Technical complications of mechanical interventions (duration of study)<br>• Line associated thrombosis (duration of study) |
| **Study design** | Randomised controlled trials (RCTs), systematic reviews of RCTs. |

## 20.3 Clinical evidence

One study which compared the effectiveness of different prophylaxis treatments for people admitted to critical care units was included in the previous guideline (CG92) [54]. However, this study was excluded from the update because the inclusion criteria reported in the study was not appropriate for this review. Patients included in this study previously had a DVT event or presence of signs of a DVT at inclusion.

A search was conducted for randomised trials comparing the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people admitted to the critical care units. Two randomised controlled trials were included [39] [192] these are summarised in Table 118 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 119 and Table 120). See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

**Table 118: Summary of studies included in the review**

| Study | Intervention and comparison | Population | Outcomes |
|---|---|---|---|
| Cook 2011 [39] | Intervention (n=1873):<br>LMWH, dalteparin, 5000IU once daily (standard dose), subcutaneously administered. Research pharmacists prepared identical syringes for subcutaneous injection of either dalteparin once daily plus placebo once daily (details about the placebo used is not reported). Participants received prophylaxis for | n= 3746<br><br>People who remained in ICU for at least 3 days<br><br>Diagnosis on admission:<br>Cardiovascular condition – 9.0%<br>Respiratory condition – 45.6%<br>Gastrointestinal condition – 14.0%<br>Renal condition – 1.74% | Mortality in ICU and hospital (up to 100 days)<br><br>DVT (at time of death, discharge or at 100 days if patients were still hospitalised): Baseline screening for DVT was diagnosed using ultrasonography. The assumption was made that ultrasonography was also used to detect DVT at the reported time points. |

| Study | Intervention and comparison | Population | Outcomes |
|---|---|---|---|
| | duration of stay in ICU.<br><br>Comparison (n=1873):<br>UFH, 5000IU twice daily, subcutaneously administered. Participants received prophylaxis for duration of stay in ICU. | Neurologic condition – 6.14%<br>Sepsis – 14.73%<br>Metabolic condition – 3.87%<br>Other medical condition – 1.74%<br>Other surgical condition – 3.16%<br><br>Age (range): 44.6-78.1<br>Gender (male to female ratio): 1.32:1<br><br>Canada, Australia, Brazil, Saudi Arabia, USA and the UK | PE (at time of death, discharge or at 100 days if patients were still hospitalised): defined as characteristic intraluminal filling defect on computed tomography of the chest, a high probability ventilation-perfusion scan, or autopsy finding.<br><br>Major bleeding (at time of death. discharge or at 100 days if patients were still hospitalised): defined as haemorrhage occurring at a critical site (e.g. intracranial haemorrhage), resulting in the need for a major therapeutic intervention (e.g. surgery), causing hemodynamic compromise, requiring at least 2 units of red-cell concentrates, or resulting in death.<br><br>Heparin induced-thrombocytopenia (at time of death. discharge or at 100 days if patients were still hospitalised) |
| Vignon 2013 [192] | Intervention (n=205):<br>Intermittent pneumatic compression (IPCD) devices and AES. IPC was achieved with using a compression system with adapted tubing sets and thigh (half-leg) sleeves. AES consisted of thigh-length AES. Participants received prophylaxis for 6 days.<br><br>Comparison (n=202):<br>AES only, thigh-length AES. Participants received prophylaxis for 6 days. | n= 407<br><br>People admitted to ICU with a high risk of bleeding<br><br>Contraindicated to pharmacological prophylaxis<br><br>Primary admission diagnostic category (%):<br>Spontaneous intracranial haemorrhage - 36%<br>Traumatic intracranial haemorrhage - 21.4%<br>Multisystem trauma - 10.8%<br>Other haemorrhage - 9.9% | DVT (symptomatic and asymptomatic): assessed using compression ultrasonography<br><br>PE, symptomatic (6 days): no definition reported<br><br>Fatal PE (6 days): no definition reported |

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| Study | Intervention and comparison | Population | Outcomes |
|---|---|---|---|
| | | Severe sepsis or septic shock - 9.6%<br>Acute respiratory distress syndrome - 5.9%<br>Other diagnoses - 6.4%<br><br>Age (mean): 55.4 years<br>Gender (male to female ratio): 1.96:1<br><br>France | |

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### 20.3.1 LMWH (standard dose; standard duration) versus UFH in people admitted to ICUs

**Table 119: Clinical evidence summary: LMWH (standard dose; standard duration) versus UFH**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with UFH | Risk difference with LMWH (95% CI) |
| All-cause mortality | 3746 (1 study) up to 100 days | MODERATE[b] due to indirectness | RR 0.91 (0.84 to 0.99) | 407 per 1000 | 37 fewer per 1000 (from 4 fewer to 65 fewer) |
| DVT (symptomatic and asymptomatic) | 3746 (1 study) at time of death, discharge or at 100 days if patients were still hospitalised | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 0.86 (0.69 to 1.07) | 86 per 1000 | 12 fewer per 1000 (from 27 fewer to 6 more) |
| PE | 3746 (1 study) at time of death, discharge or at 100 days if patients were still hospitalised | LOW[b,c] due to indirectness, imprecision | RR 0.64 (0.36 to 1.16) | 15 per 1000 | 5 fewer per 1000 (from 10 fewer to 2 more) |
| Major bleeding | 3746 (1 study) at time of death, discharge or at 100 days if patients were still hospitalised | LOW[b,c] due to indirectness, imprecision | RR 0.98 (0.75 to 1.28) | 56 per 1000 | 1 fewer per 1000 (from 14 fewer to 16 more) |
| Heparin-induced thrombocytopenia | 3746 (1 study) at time of death, discharge or at 100 days if patients were still hospitalised | LOW[b,c] due to indirectness, imprecision | RR 0.42 (0.15 to 1.18) | 6 per 1000 | 4 fewer per 1000 (from 5 fewer to 1 more) |

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

### 20.3.2 People who are contraindicated to pharmacological prophylaxis

**Table 120: Clinical evidence summary: IPCD (half-leg) and AES versus AES**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with AES only | Risk difference with IPCD + AES (95% CI) |
| DVT (symptomatic and asymptomatic) | 362 (1 study) 6 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | RR 0.64 (0.3 to 1.37) | 87 per 1000 | 31 fewer per 1000 (from 61 fewer to 32 more) |
| PE | 406 (1 study) 6 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | Peto OR 0.13 (0 to 6.75) | 5 per 1000 | 4 fewer per 1000 (from 5 fewer to 28 more) |
| Fatal PE | 406 (1 study) 6 days | VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision | [d] | [d] | 0 fewer per 1000 (from 10 fewer to 10 more)[d] |

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
c Downgraded by 1 increment if the outcome definition reported did not meet definition of outcome in protocol
d Zero events in both arms. Risk difference calculated in Review Manager.

## 20.4 Economic evidence

**Published literature**

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

## 20.5 Evidence statements

**Clinical**

LMWH at a standard dose for a standard duration was compared with UFH, the outcomes all-cause mortality, DVT (symptomatic and asymptomatic), PE, major bleeding and heparin-induced thrombocytopenia were reported in one study. There was clinical benefit of LMWH in terms of all-cause mortality, possible clinical benefit of LMWH in terms of PE and heparin-induced thrombocytopenia, although all these findings could also be consistent with no difference. There was no clinical difference in terms of DVT (symptomatic and asymptomatic) and major bleeding, however there was some uncertainty around these results. The quality of the evidence ranged from very low to moderate due to risk of bias, indirectness and imprecision.

*People who are contraindicated to pharmacological prophylaxis*

IPCD (half-leg) in combination with AES was compared with AES, the outcomes DVT (symptomatic and asymptomatic), PE and fatal PE were reported in one study. There was possible clinical benefit of IPCD in combination with AES in terms of DVT (symptomatic and asymptomatic) and PE. However the uncertainty around these results means they are also consistent with no difference or clinical harm. There was no clinical difference in terms of fatal PE. The quality of the evidence was very low due to risk of bias, indirectness and imprecision.

**Economic**

- No relevant economic evaluations were identified.

## 20.6 Recommendations and link to evidence

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| **Recommendations** | **1.4.17 Assess all people admitted to the critical care unit for risk of VTE and bleeding. [2018]**<br><br>**1.4.18 Provide LMWH[bbbb] to people admitted to the critical care unit if pharmacological VTE prophylaxis is not contraindicated. For people with renal impairment see recommendations 1.4.7 and 1.4.8. [2018]**<br><br>**1.4.19 Consider mechanical VTE prophylaxis for people admitted to the critical care unit if pharmacological prophylaxis is contraindicated based on their condition or procedure. [2018]** |

[bbbb] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

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| | **1.4.20 If using mechanical VTE prophylaxis for people admitted to the critical care unit, start it on admission and continue until the person no longer has reduced mobility relative to their normal or anticipated mobility. [2018]**<br><br>**1.4.21 Reassess VTE and bleeding risk daily for people in critical care units. [2018]**<br><br>**1.4.22 Assess VTE and bleeding risk more than once a day in people admitted to the critical care unit if the person's condition is changing rapidly. [2018]** |
| **Research recommendation** | **None** |
| Relative values of different outcomes | The committee considered all-cause mortality (up to 90 days after leaving ICU), deep vein thrombosis (symptomatic and asymptomatic) (7–90 days after leaving ICU), pulmonary embolism (7–90 days after leaving ICU), major bleeding (up to 45 days after leaving ICU) and fatal PE (7–90 days after leaving ICU) as critical outcomes.<br>The committee considered clinically relevant non-major bleeding (up to 45 days after leaving ICU), health-related quality of life (up to 90 days after leaving ICU), heparin-induced thrombocytopenia (duration of study), technical complications of mechanical interventions (duration of study) and line associated thrombosis (duration of study) as important outcomes.<br>Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes. |
| Quality of the clinical evidence | Two randomised controlled trials were included in this review. One of these studies evaluated the use of LMWH (dalteparin) versus unfractionated heparin (UFH) for people admitted to critical care units. The quality of the evidence ranged from very low to moderate. Evidence was downgraded due to risk of bias, indirectness and imprecision. Outcomes were downgraded for indirectness due to an inappropriate time point, past the time-point set by the committee (up to 90 days after leaving ICU).<br>The other included study evaluated the use of IPCD with AES versus AES alone. The quality of the evidence ranged from very low to low due to risk of bias, indirectness and imprecision. |
| Trade-off between clinical benefits and harms | This is a critically ill population where survival is the most immediate concern. Patients may be admitted into critical care from different wards within the hospital, representing a worsening of the person's condition. Therefore it is important to reassess the person's risk on admission to ICU as risk may differ from first assessment and the clinical condition may have changed. Critical care is a recognised risk factor for increasing VTE risk (it is a factor in both the Department of Health risk assessment list and risk tools such as the 7-factor version of IMPROVE) and as such the committee considered that in absence of bleeding risk factors and after taking into account planned interventions or therapies which may increase complications, VTE prophylaxis should be offered. Moderate quality evidence showed a clinically important difference in mortality rate in those offered LMWH compared to those offered UFH. No evidence was identified for any other pharmacological intervention. Therefore the committee felt comfortable recommending LMWH for this population. The committee noted that renal impairment is a concern within this population and advise clinicians to refer to the renal impairment recommendation when applicable. Due to the high VTE risk in this population, if people were contraindicated for |

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| | pharmacological prophylaxis, the committee recommended considering mechanical prophylaxis.<br><br>As the clinical situation changes it is necessary to reassess the risks of VTE and bleeding. For this reason the committee did not state a recommended duration for LMWH as they considered it would be up to clinical judgement based on the daily reassessment of changing VTE and bleeding risk. |
| Trade-off between net clinical effects and costs | No economic studies were included for this population. Unit costs of pharmacological and mechanical prophylaxis were presented to the committee (see appendix Q). The committee acknowledged that there will be a cost impact given the need for more staff time to complete the assessment on admission to the critical care unit, but this will be off-set by the potential benefits for reducing the risk of having a costly VTE event. The committee noted that the clinical evidence showed a clinical benefit for LMWH versus UFH in terms of PE, heparin-induced thrombocytopenia and mortality and considered that the higher cost of using LMWH would be offset by the downstream cost saving from averted PEs and HIT.<br><br>For people in whom pharmacological options are contraindicated, the committee considered that the evidence available supported the use of mechanical prophylaxis given the high risk of VTE in this population. |
| Other considerations | Patients treated in the critical care unit may be unconscious or not capable of making decisions about their treatment. In such situations, decisions about care should take into account the known view of patients and discussions with family members, where appropriate. |

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