GUIDELINES

Indian Society of Critical Care Medicine Consensus Statement for Prevention of Venous Thromboembolism in the Critical Care Unit

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Abstract

Deep vein thrombosis (DVT) is a preventable complication of critical illness, and this guideline aims to convey a pragmatic approach to the problem. Guidelines have multiplied over the last decade, and their utility has become increasingly conflicted as the reader interprets all suggestions or recommendations as something that must be followed. The nuances of grade of recommendation vs level of evidence are often ignored, and the difference between a "we suggest" vs a "we recommend" is overlooked. There is a general unease among clinicians that failure to follow the guidelines translates to poor medical practice and legal culpability. We attempt to overcome these limitations by highlighting ambiguity when it occurs and refraining from dogmatic recommendations in the absence of robust evidence. Readers and practitioners may find the lack of specific recommendations unsatisfactory, but we believe that true ambiguity is better than inaccurate certainty. We have attempted to comply with the guidelines on how to create guidelines.[1] And to overcome the poor compliance with these guidelines.[2] Some observers have expressed concern that DVT prophylaxis guidelines may cause more harm than good.[3] We have placed greater emphasis on large randomized controlled trials (RCTs) with clinical end point and de-emphasized RCTs with surrogate end points and also de-emphasized hypothesis generating studies (observational studies, small RCTs, and meta-analysis of these studies). We have de-emphasized RCTs in non-intensive care unit populations like postoperative patients or those with cancer and stroke. We have also considered resource limitation settings and have avoided recommending costly and poorly proven therapeutic options.

Keywords: Acute pulmonary embolism, Deep vein thrombosis, Guidelines, Intensive care unit mortality.

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Executive Summary

Preamble

Deep vein thrombosis is a preventable complication of critical illness, and this consensus statement aims to convey a pragmatic approach to the problem based on the combination of evidence and agreement among all committee members.

Guidelines have multiplied over the last decade, and their utility has become increasingly conflicted as the reader interprets all suggestions or recommendations as something that must be followed. The nuances of the grade of recommendation vs the level of evidence are often ignored, and the difference between a "we suggest" vs a "we recommend" is overlooked. There is a general unease among clinicians, that failure to follow the guidelines translates to poor medical practice and legal culpability.

An expert panel consisting of experienced intensivists was formed to critically appraise the available literature on prevention of venous thromboembolism (VTE) in critically ill patients. We attempted to overcome the above-mentioned limitations of guidelines by highlighting ambiguity when it occurs and refraining from dogmatic recommendations in the absence of robust evidence. Readers and practitioners may find the lack of specific recommendations unsatisfactory, but we believe that true ambiguity is better than inaccurate certainty. We have attempted to comply with the guidelines on how to create guidelines[1] and to overcome the poor compliance with these guidelines.[2] Some observers have expressed concern that DVT prophylaxis guidelines may cause more harm than good.[3] We have placed

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greater emphasis on large RCTs with clinical end point on the topic and understated RCTs with having DVT as surrogate end points and also downplayed hypothesis generating studies (observational studies, small RCTs, and meta-analysis of these studies). We have dismissed RCTs conducted in non-intensive care unit (ICU) populations like postoperative patients or those with cancer and stroke. We have also considered resource-limited settings and avoided recommending costly and poorly proven therapeutic options.

Accordingly, we have recommended practices that have demonstrated clinical benefit or absence of benefit, in large RCTs with clinical end points, of VTE, or complications due to use of prophylactic therapy. The commonest studied surrogate end point in trials is DVT diagnosed by venous Doppler or some other investigation. The clinically relevant primary outcomes in studies include symptomatic DVT, symptomatic pulmonary embolism (PE), mortality, and bleeding as the secondary outcome.

Each member of the expert panel was asked to give a strong recommendation or a conditional recommendation for each relevant clinical decision. For conditional recommendations, the rationale for this has been stated (plausible but minimal data or no clinical outcome data). These recommendations are restricted to the prevention of VTE (DVT and PE) in adult critically ill patients. We have excluded diagnosis or treatment of DVT and PE and pediatric population.

The panel will attempt to update the recommendations on a regular basis, but at the same time, readers should keep themselves apprised with the fast-emerging data.

Descriptive Review

The approach to DVT prevention essentially requires two separate risk evaluations, the risk of DVT vs the risk of bleeding. Prophylaxis is strongly indicated when the risk of thrombosis is high with low bleeding risk, and DVT prophylaxis with use of anticoagulants must be avoided in those with low DVT risk and high bleeding risk. DVT prophylaxis options include early passive and active mobilization, and use of pharmacological agents and mechanical devices. Clinicians should institute appropriate DVT prophylaxis as per the perceived risk of DVT vs the perceived risks of pharmacological agents.

Summary of Recommendations

A. General Considerations

1. Risk Stratification

1.1 All critically ill patients in the ICU should be considered to be at moderate to high risk for DVT.

We are unable to recommend the use of any specific scoring systems or cutoff values of any of the scoring systems for risk stratification of DVT in critically ill patients. However, we recommend considering the presence of following factors as high risk for development of VTE in ICU patients: Use of mechanical ventilation, need for vasopressors, platelet transfusion, presence of septic shock, use of a central venous catheter (CVC), use of sedatives and paralytic agents, age >60 years, prolonged immobilization, end-stage renal disease (ESRD), longer length of ICU stay (≥3.5 days).

Patients having even one of the above-listed factors should be considered at a higher risk for developing DVT, and more the number of factors present, the risk is considered to be higher.

Strong recommendation given by all *11 panelists.*

1.2 All patients should be evaluated for bleeding risk. As there is no bleeding risk scoring system which is validated for ICU patients, the panel recommends analysis of the number of bleeding risk factors by obtaining a detailed history, clinical examination, and investigation.

Bleeding risk increases with presence of coagulopathy (platelets <50,000/cmm, INR >1.5, aPTT >1.5 times the normal), a recent or scheduled planned/emergency procedure or surgery, presence of recent or ongoing bleeding episodes, and risk of bleed in a vital area like the airway, intraocular, or the central nervous system (CNS).

Strong recommendation given by all *11 panelists.*

2. Choice of Prophylaxis

2.1 All critically ill patients should receive pharmacological thromboprophylaxis for DVT prevention if the ratio of DVT risk to risk of bleeding is acceptable, and there is no other contraindication.

Strong recommendation is given by eight panelists. Three panelists chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data of development of DVT in the absence of chemoprophylaxis.

2.2.1 Panel recommends using either unfractionated heparin (UFH) low-molecular-weight heparin (LMWH) or Fondaparinux for DVT prophylaxis.

Strong recommendation is given by seven panelists. The remaining four panelists chose to give a conditional recommendation in the absence of adequate evidence on clinical outcome data.

2.2.2 For acute critically ill patients, LMWH are preferred over direct oral anticoagulants (DOACs) for DVT prophylaxis.

Strong recommendation is given by nine panelists. Two panelists chose to provide a conditional recommendation in the absence of adequate evidence on clinical outcome data.

2.3.1 In critically ill medical patients who cannot receive pharmacological VTE prophylaxis because of some contraindication, the panel recommends using mechanical method of thromboprophylaxis [intermittent pneumatic compression (IPC) device or graduated compression stockings (GCS)].

Strong recommendation is given by eight panelists. Three panelists chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data.

2.3.2 The panel recommends using IPC devices as the choice for mechanical thromboprophylaxis for VTE. If IPC is not available, use GCS.

Strong recommendation is given by eight panelists but rest three chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data.

2.4 Panel recommends against the routine use of combined mechanical plus pharmacological prophylaxis for DVT prevention.

Strong recommendation agreed by all 11 panelists.

2.5 VTE prophylaxis should continue until the patient is discharged from the ICU.

Strong recommendation is given by six panelists but the remaining five panelists chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data.

2.6.1 Routine placement of endovascular (IVC) filters for prevention of thromboembolism, in patients with proximal DVT cannot be recommended.

Strong recommendation agreed by all 11 panelists.

2.6.2 Panel encourages patients to mobilize as soon as possible post-DVT, as it may be associated with lesser complications.

Strong recommendation is given by nine panelists, but two of the panelists said it is plausible, and due to poor literature, they gave a conditional recommendation.

B. Special Considerations

3.1 Panel recommends using the subclavian vein (SV) as a preferred site for insertion for central venous catheters to prevent DVT followed by internal jugular vein (IJV). Femoral vein (FV) should be chosen as the least preferred site for the same reason. Consider all other risk factors associated with various sites for central venous cannulation before deciding upon the site of cannulation.

Strong recommendation is given by seven panelists. The remaining four chose to give a conditional recommendation due to nonavailability of adequate evidence from large clinical trials and meta-analysis.

3.2 In patients of trauma, the panel recommends the initial use of mechanical prophylaxis for DVT prevention in severe trauma (including traumatic brain injury [TBI], spinal cord injury, blunt abdominal trauma). Once the risk of increase in size of hematoma/onset of fresh bleeding has been judged to be acceptable, chemical prophylaxis can be considered after 24–48 hours of ICU admission.

Strong recommendation is given by seven panelists. The remaining four chose to give a conditional recommendation as evidence from large clinical trials and meta-analysis is lacking.

3.3 Panel recommends early use of UFH or LMWH in critically ill surgical patients. Mechanical prophylaxis should be used until the risk of bleeding is high, postsurgery.

Strong recommendation is given by all 11 panelists.

3.4 Panel recommends initiating pharmacological VTE prophylaxis as quickly as feasible after high-risk cardiac surgical procedures for patients with no risk of life-threatening bleeding.

Strong recommendation is given by eight panelists. The remaining three chose to give a conditional recommendation as clinical outcome data is insufficiently convincing.

3.5 Patients with sepsis must receive daily chemoprophylaxis against DVT. Chemoprophylaxis includes once daily LMWH vs twice or thrice daily UFH.

Strong recommendation is given by all 11 panelists.

3.6 In patients with renal failure, prophylactic anticoagulation therapy for a short duration for DVT and VTE is recommended, the decision to proceed to a prolonged therapeutic anticoagulation needs to be critically evaluated individually.

In critically ill patients with renal failure, especially with a creatinine clearance of <30 mL/minute, use of UFH or Dalteparin or any LMWH that has a low degree of renal metabolism, must be preferred.

Strong recommendation is given by all 11 panelists.

3.7 All patients with heart failure with a low bleeding risk should receive LMWH or Fondaparinux.

Strong recommendation is given by nine panelists but the remaining two chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data.

3.8.1 In case of ischemic stroke, chemical prophylaxis should be initiated for all the patients with low bleeding risk, within 24 hours of admission.

Strong recommendation is given by three panelists but the remaining eight chose to give a conditional recommendation due to absence of adequate evidence on clinical outcome data.

3.8.2 In cases of hemorrhagic stroke and neurosurgical patients, chemical prophylaxis can be considered after 24–48 hours and after clinical, radiological, and neurosurgical review.

Strong recommendation is given by three panelists but the remaining eight chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data.

3.9 All critically ill pregnant patients should receive thrombo-prophylaxis with LMWH or UFH if the risk of bleeding is low. In those with a high bleeding risk, use of mechanical device for DVT prophylaxis should be considered.

Strong recommendation is given by all 11 panelists.

3.10.1 All severe and critically ill COVID-19 patients have a high risk of VTE, thus use of pharmacological prophylaxis of VTE is strongly recommended, in the absence of contraindications.

Strong recommendation is given by all 11 panelists.

3.10.2 In severe or critically ill COVID-19 patients at high risk of bleeding or with active bleeding contraindicating temporarily pharmacological thromboprophylaxis, it is recommended to use mechanical prophylaxis for VTE prevention.

Strong recommendation is given by all 11 panelists.

3.10.3 We recommend use of standard anticoagulation dose for prevention of VTE in critically ill patients with COVID-19 disease. All severe and critically ill COVID-19 patients have a high risk of VTE, so prevention of VTE is strongly recommended in absence of contraindication.

Strong recommendation is given by all 11 panelists.

A. General Considerations

1. Risk Stratification in a Critically Ill Patient

Varied scoring systems have been used to assess the risk of VTE in a hospitalized patient and the risk of bleeding associated with pharmacological prophylaxis for DVT. Also, the development of DVT is potentially life-threatening[4] for critically ill patients on mechanical ventilator, in cardiac and respiratory failure, or in shock, as the occurrence of PE in this set of patients will decompensate the already compromised system.

1.1 DVT Risk Stratification (Table 1):

Due to the heterogeneity of ICU population studied in various studies, it is difficult to identify precisely which ICU patients are vulnerable to develop a DVT. No validated risk stratification score has been developed till date, specific for ICU patients.

The complex, 30-item Caprini model applied in the PROF-ETEV trial[5] for risk stratification of 777 critically ill patients calculated that 83% of ICU patients were in the "very high risk" category (8.5–11.6% in-hospital incidence of VTE). A retrospective cohort analysis of 4,844 patients,[6] validated using this model in surgical ICU patients, with lower scores corresponding with a lesser risk of VTE, and higher scores (>8) corresponding with higher risk; However, it does not include the specific risk factors of DVT in ICU like mechanical ventilation, shock, blood transfusion, platelet transfusion, and presence of CVC. Similar findings were found in a retrospective cohort study of 2,127 cancer patients admitted to the post-surgical ICU, with patients having a Caprini score >10 at highest risk of VTE.[7]

Others score like Padua Prediction Score, The Geneva Risk Score, and International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) Risk Score have been studied in medical patients but still do not cover all the risk factors of critically ill patients (Table 2).[8–10]

Cook et al.[11] studied 261 patients with a mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 25.5, in a prospective cohort analysis and found the DVT prevalence as 2.7% in ICU admission, with the DVT incidence of 9.6%.

Four risk factors were identified for ICU-acquired DVT:

1. Personal or family history of VTE,
2. Vasopressor use,
3. End-stage renal failure, and
4. Platelet transfusion.

Also patients with DVT were found to have a longer duration of mechanical ventilation and longer length of ICU and hospital stay, compared to the patients without DVT.[11]

However, Kaplan et al.[12] found a much higher incidence of DVT (37.2%) in a multicenter prospective study of 113 patients with severe sepsis. Seventy-seven percent of the patients included were on MV and 54% required vasopressors with an average APACHE II score of 18.2. Patients were either on chemoprophylaxis (80.5%), warfarin (2.7%), or sequential compression devices (SCDs). The overall incidence of VTE (all lower and upper limb DVT and symptomatic) was seen in 37.2%, with 3.5% of symptomatic PE (with or without DVT). Sepsis-induced marked proinflammatory and prothrombotic systemic milieu is the probable cause of higher incidence of VTE in this group.[12]

DETECT-DVT[13] registry found an incidence of DVT in nine out of 278 patients. Seven out of these nine patients had not received any thromboprophylaxis, with data missing for the remaining two patients. The authors encourage use of thromboprophylaxis in DVT prevention and implementation of internal audits in hospitals to monitor and control the incidence of symptomatic DVT in Indian septic patients.[13]

Another cohort of 3,746 medical and surgical critically ill patients found a 7.7% incidence of VTE, despite receiving pharmacological thromboprophylaxis with either LMWH or UFH at standard doses. They reported increased body mass index (BMI), a personal or family history of VTE, and being on vasopressors as independent risk factors for failure of thromboprophylaxis.[14]

A recent systematic review and meta-analysis or VTE[15] found a probable association of VTE with moderate certainty, with older age (>60 years); elevated C-reactive protein >10 mg/L, D-dimer >500 ng/mL at baseline, and fibrinogen levels (>400 mg/dL); tachycardia (>100 beats/minute); thrombocytosis (>350 × 10^9/L); leukocytosis (>11 × 10^9/L); fever (temperature >38–39.5°C); leg edema; lower Barthel Index score (≤9); immobility (confinement to bed for >72 hours or >7 days or bedridden or nonambulatory); paresis; previous history of VTE; thrombophilia (familial or acquired disorder of the hemostatic system); malignancy; critical illness; and infections (including cellulitis, pneumonia, and sepsis).

Viarasilpa et al.[16] have designed a prediction score (the ICU-VTE score) after obtaining data from 37,050 patients in a retrospective cohort study. The score consisted of six independent predictors: presence of CVC (5 points), more than or equal to 4 days of immobilization (4 points), prior history of VTE (4 points), mechanical ventilation (2 points), lowest hemoglobin during hospitalization greater than or equal to 9 gm/dL (2 points), and platelet count at admission greater than 250,000/μL (1 point). A score of 0–8 was found to have a low (0.3%) risk of VTE, whereas a score of 9–14 (22%) and 15–18 (2%) were considered to be intermediate (3.6%) and high risk (17.7%) for VTE, respectively.

However, the vast majority of critically ill patients should be assumed to be at a moderate to high risk for DVT.[17–19]

We do not recommend the use of any specific cutoff values of any scoring system for risk stratification of DVT. Following factors should be considered in addition to other scoring systems when risk stratifying a critically ill patient for VTE:

- Mechanical ventilation
- Need of vasopressors
- Platelet transfusion
- Septic shock
- Use of CVC
- Use of sedatives and paralytic agents
- Prolonged immobilization (≥4 days)
- ESRD
- Longer length of stay in the ICU (≥3.5 days)[20]
- Age >60 years[15]
- Past history suggestive of DVT
- Increased BMI (>40 kg/m^2)

Patients having even one of the above factors should be considered at an increased risk for VTE, and more the factors, greater is the risk for development of VTE.

Recommendation

1.1 All critically ill patients in the ICU should be considered to be at moderate to high risk for DVT.

Strong recommendation is given by all 11 panelists.

1.2 Bleeding risk stratification

It is required to evaluate the patient for the probable bleeding risk before starting prophylactic anticoagulation. Detailed history concerning risk factors for bleeding must be obtained from every patient planned for VTE chemoprophylaxis. Data to estimate chances of bleeding in critically ill patients is limited, and most clinical data come from studies on patients receiving therapeutic anticoagulation mainly for atrial fibrillation. Very few studies have evaluated the same in patients receiving prophylactic anticoagulation, but none of them have been extensively studied in ICU patients.

Kuijer et al. proposed a bleeding risk prediction score to be calculated to be instituted before starting anticoagulation in patients with VTE. The score could be calculated with three easily obtainable clinical variables (age, sex, malignancy), and patients with a score more than 3 were considered to be at a high bleeding risk.[21]

Table 1: Lists various studies predicting risk of DVT[5,11,12]

Study	*Design*	*Patients*	*Aim/objective*	*Risk factors for DVT*	*Conclusion*	*Limitations*
PROF-ETEV trial (Garcia-Olivarez et al., 2014)	Single-day point prevalence	777 total 62% medical 30% surgical and 7% trauma	High risk/moderate/low risk of DVT	Vasopressor Acute cardiac and respiratory pathology Mechanical ventilation	High risk of DVT but low rate of appropriate prophylaxis	Limited factors studied
Cook et al. (2005)	Prospective cohort	261	Prevalence of incidence and risk factors for proximal DVT	Personal/family history • ESRD • Platelet transfusion • Vasopressor	Medical-surgical critically ill are at risk of DVT	Trauma and orthopedic patients not involved
Kaplan et al. (2015)	Multicenter and prospective	113	Sepsis is risk factor for DVT?	Presence of CVC ICU-stay Age Mechanical ventilation need	Severe sepsis and septic shock have high incidence of VTE	Small size Previous history of DVT not included Severe sepsis is outdated now

Table 2: Lists the DVT risk predicting scores[8–10]

Factors	*Padua Prediction Score*	*The Geneva Risk Score (revised)*	*IMPROVE and IMPROVED Risk Score*
Previous VTE	✓	✓	✓
Malignancy	✓	✓	✓
Mobility	✓		✓ paralysis
Thrombophilia	✓		✓
Age	✓ 70	✓ 65	✓
Hemoptysis	✓	✓	
Mechanical ventilation	×	×	×
Platelet transfusion	×	×	×
Vasopressor	×	×	×
Renal failure	×	×	×
Surgery or fracture within 1 month	✓	✓	
Unilateral lower limb swelling	✓	✓	
Obesity	✓ BMI>30		
Ongoing hormonal treatment	✓		
Pain on palpitation	✓	✓	
Heart/respiratory failure	✓		
D-dimer			✓
ICU admission			✓
Heart rate		✓ 75–94/minute	
Limitations with scoring system	Yet to validate in large prospective study	Not to diagnose but to guide work-up and testing of PE and not DVT	Only limited factors are studied

RIETE Registry identified six independent variables for identifying the risk of major bleeding within 3 months of administering anticoagulant therapy in patients with acute VTE—age >75 years, recent bleeding, cancer, creatinine >1.2 mg/dL, anemia, and PE on presentation.[22]

Decousus et al.[23] assessed 15,156 acutely ill medical patients in a multinational cohort taken from IMPROVE and detected a cumulative incidence of bleeding (both major and nonmajor bleeding) as 3.2%, within 14 days of hospital admission. Eleven risk factors detected at hospital admission were independently associated with increased bleeding events: active gastroduodenal ulcer, bleeding during the 3 months prior to admission, platelet count $<50 \times 10^9$ at admission, advanced age ≥85 years, ICU stay, active malignancy, male sex, CVC usage, rheumatic disease, liver failure, and renal failure.[23] These risk factors were consolidated together to form a new IMPROVE bleeding risk score, which helps to predict the risk of clinically important bleeding at hospital admission for an individual patient (Tables 3 and 4).

Despite few limitations, IMPROVE bleeding score helps identify high-risk patients with a score of >7, and these are the patients we need to be cautious about. However, further validation of this score is required in critically ill patients.

Another retrospective analysis[24] of a large database of 327,578 nonsurgical patients ≥40 years of age with ≥2 days of hospitalization found major bleeding rate of 1.8% and minor bleeding risk of 7.1%. Strong predictors identified for major bleeding were preindex

Table 3: Factors in IMPROVE bleeding score (acutely ill medical patients)[23]

Risk factors	*Points*
Moderate renal failure (GFR 30–59 vs >60 mL/minute/m^2)	1
Male vs Female	1
Age, 40–84 vs <40	1.5
Current cancer	2
Rheumatic disease	2
Central venous catheter	2
ICU/CCU	2.5
Hepatic failure	2.5
Age >85	3.5
Platelet count <50,000	4
Bleeding 3 months before admission	4
Active gastroduodenal bleeding	4.5

Table 4: Rate of bleeding varies as per the IMPROVE score[23]

Risk score	*Percentage of bleeding*
1	0.5%
4	1.6%
7	4.1%
15	14%

gastroduodenal ulcer, thromboembolic stroke, blood dyscrasias, liver disease, and rehospitalization. Other minor predictors identified were higher age, group male gender, and hospital stay of ≥3 days.

A retrospective cohort study[25] of 3,358 cancer patients found gastrointestinal cancer site, an admission for anemia, morbid obesity (BMI ≥40), thrombocytopenia (<150,000/mm^3), and low hemoglobin on admission, as risk factors on admission for bleeding.

A meta-analysis[15] of three studies including 160,142 patients found a probable association with the following factors for the risk of bleeding with moderate certainty: older age (≥65 years), sex (male), anemia as reason for admission, morbid obesity (≥40 kg/m^2), low hemoglobin (<13 g/dL in men and <11.5 g/dL in women), gastroduodenal ulcers, rehospitalization, critical illness, thrombocytopenia (<50 × 10^9/L), blood dyscrasias (presence of any bleeding disorder on admission), hepatic disease, renal failure, antithrombotic medication, and presence of a CVC.

Recommendation

1.2 All patients should be evaluated for bleeding risk. As there is no bleeding risk scoring system which is validated for ICU patients, the panel recommends analysis of the number of bleeding risk factors by obtaining a detailed history, clinical examination, and investigation.

Strong recommendation is given by all 11 panelists.

Risk factors for bleeding include:

- Presence of coagulopathy (platelets <50,000/cmm, INR >1.5, aPTT >1.5 times the normal),
- A recent or scheduled elective/emergency procedure or surgery,
- Presence of recent or ongoing bleeding episodes, and
- Risk of bleed/active bleed in critical areas like the airway, intraocular, or the CNS.
- Admission for anemia
- Hepatic or renal disease
- Older age (>65 years)
- BMI (>40 kg/m^2)

2. Choice of Prophylaxis

2.1 Selection of Patient

The best assessment model for risk assessment of VTE vs the risk of bleeding has not yet been defined. Choice of thromboprophylaxis should evaluate the potential risk of VTE in a critically ill patient, along with the risk for bleeding. Although it is a daily struggle to maintain a difficult balance between bleeding and thrombosis, a meticulous decision considering all factors should be taken.

However, the vast majority of ICU patients should be assumed to be at a moderate to high risk for DVT.[17–19] Also, not receiving early thromboprophylaxis without obvious reasons, within the first 24 hours of ICU admission, has been shown to have a higher risk of mortality.[4]

Alhazzani et al.[26] conducted a meta-analysis of all critically ill patient trials who received heparin prophylaxis. A total of 7,226 patients were studied in a total of seven trials, and it was clear that compared with placebo, any heparin thromboprophylaxis reduced the rates of DVT [pooled risk ratio, 0.51 (95% CI, 0.41, 0.63); p <0.0001; I = 77%] and PE [risk ratio, 0.52 (95% CI, 0.28, 0.97); p = 0.04; I = 0%] but not symptomatic DVT [risk ratio, 0.86 (95% CI, 0.59, 1.25); p = 0.43]. The risk of major bleeding and of mortality was same in both the groups.

Recommendation

2.1 All critically ill patients should receive pharmacological thromboprophylaxis for DVT prevention if the ratio of DVT risk to the risk of bleeding is acceptable, and there is no other contraindication.

Strong recommendation is given by eight panelists but remaining three panelists chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data of development of DVT in absence of chemoprophylaxis.

2.2 Selection of Chemical Thromboprophylaxis

Choosing the right agent for thromboprophylaxis is also an important factor to be considered in sick, critically ill patients. Factors such as ease of administration and presence of organ failures are to be taken into consideration. Not many trials have shown an advantage of one agent over another, and a decision based on host factors and hospital policy should be taken. (Table 5 lists the doses of commonly used drugs for thromboprophylaxis in the ICU). Also to take into consideration the ease of monitoring of response in unstable patients, especially with the use of LMWH, as a poor response can lead to a failed prophylaxis.

In an RCT of 156, critically ill patients undergoing elective surgery were randomized to receive LMWH 40 mg, once daily and a placebo injection, vs UFH 5000 IU twice daily. Each patient was postoperatively confirmed clinically and with an ultrasound Doppler for the presence of DVT. Of the 156 patients in total, there was no difference in efficacy of LMWH vs Heparin. However, minor complications like hematoma and surgical site infection were more in the heparin group.[27]

Table 5: Commonly used drugs for DVT prophylaxis

Drug	*Dose*	*Route*
Unfractionated heparin	5000 units	Subcutaneous, twice daily
Enoxaparin	40 mg	Subcutaneous, once daily
Dalteparin	5000 IU	Subcutaneous, once daily
Fondaparinux	2.5 mg	Subcutaneous, once daily

Cook et al.[28] conducted a multicenter RCT of 3,764 patients comparing Dalteparin once daily, plus Placebo once daily vs UFH 5000 IU twice daily for VTE prophylaxis. They found a reduction in PE (1.3 vs 2.3%, $p = 0.01$), but no difference in the rate of DVT (5.1 vs 5.8%, $p = 0.57$) with dalteparin as compared with heparin.

An RCT of 3,746 medical-surgical critically ill patients (secondary analysis of PROTECT database) found no significant difference in the incidence of proximal leg DVT with Dalteparin compared with UFH. However, a significant decrease in the risk of PE was observed with the use of Dalteparin.[29]

A meta-analysis by Alhazzani et al. of seven randomized trials involving 7,226 critically ill medical-surgical patients found that use of any heparin prophylaxis compared with that of placebo decreases the rate of DVT and PE, but not of symptomatic DVT. Risk of major bleeding and mortality rates were similar with the use of UFH and LMWH. However, as compared with UFH, use of LMWH reduced the rate of PE and symptomatic PE but did not decrease the rate of DVT, symptomatic DVT, major bleeding, or mortality.[26]

Another meta-analysis of eight RCTs (5,567 patients) found a beneficial effect of LMWH over UFH, in reducing the risk of any DVT (RR 0.84, 95% CI 0.71–0.98, $p = 0.03$) with a net clinical benefit (RR 0.90, 95% CI 0.83–0.97, $p = 0.01$). No statistically significant difference was found in the risk of any PE, major bleeding, or mortality.[30]

A meta-analysis of 12 RCTs with 8,622 patients found that the risk of DVT was similar in patients receiving prophylaxis with UFH (5000 U sc bid) or LMWH (either enoxaparin sc 30 mg bid/40 mg qd) (OR, 1.16; 95% CI, 0.68–2.11). Both the treatment groups had similar major bleeding risk, even in critically ill patients with a high risk of bleeding.[31]

Recommendation

2.2.1 *Panel recommends using either UFH or LMWH or Fondaparinux for DVT prophylaxis.*

Strong recommendation is given by seven panelists but the remaining four panelists chose to give a conditional recommendation in the absence of adequate evidence on clinical outcome data.

No studies have been conducted on the use of current DOACs for VTE prevention in ICU patients. Four trials though have examined the role of DOACs in the prevention of VTE in medically ill patients—ADOPT trial, MAGELLAN trial, APEX trial, and MARINER trial.[32–35] However, all the four trials were constructed to evaluate extended vs standard duration of thromboprophylaxis and not to determine which is the best agent for prophylaxis of VTE.

DOACs may be beneficial against symptomatic VTE, all VTE; however, they also have been associated with a higher risk of bleeding numbers.[36]

Overall, there is paucity of evidence to suggest the role of DOACs in VTE prevention in the ICU.

Recommendation

2.2.2 *For acute critically ill patients, LMWH are preferred over DOACs for DVT prophylaxis.*

Strong recommendation is given by nine panelists but the remaining two panelists chose to give a conditional recommendation in the absence of adequate evidence on clinical outcome data.

2.3 Mechanical Method of Thromboprophylaxis

ICU patients who carry a high risk for VTE, with a contraindication for use of anticoagulation (active bleeding, intracranial bleed), or risk of bleeding is high (presence of coagulopathy), use of mechanical thromboprophylaxis alone may be proposed. Mechanical devices provide compression to a limb with the help of calf or thigh length garments and thus increase blood velocity in the lower limb deep veins, reducing blood stasis and also stimulating fibrinolysis. Whenever mechanical thromboprophylaxis is used, a pharmacological agent for VTE prophylaxis should be initiated as soon as the bleeding risk decreases.

Mechanical methods of DVT prophylaxis include:

- GCS—Compression stockings with graduated pressure (highest at the ankle and lower proximally) prevent venous stasis due to pressure difference.
- Intermittent Pneumatic Compression Devices (IPCD)—Alternate inflation and deflation of the cuffs tied over the calf and the thigh muscles to improve venous drainage.

  Sequential compression devices are a type of IPCDs with split pockets of inflation on the sleeves, which helps to squeeze in a "milking action." The pockets inflate sequentially starting from the most distal pockets, followed by the subsequent pockets in the same manner, to promote distal to proximal venous drainage.

  Intermittent Pneumatic Compression Devices are noninvasive, and easy to use, but more costly, and may be accompanied with discomfort, reduced mobility, and skin injury.
  Commercially available mechanical pumps have an automatic cycle, that is, there are 12 seconds for inflation for venous emptying alternating with 48 seconds for deflation to allow venous filling. The pressure varies in between 30 and 60 mm Hg.

- Mechanical foot pumps—The third type of compression device are mechanical foot pumps, which by intermittent plantar compression increase the flow of blood in the leg veins. Very rarely used.

  In cases of using mechanical prophylaxis, a Cochrane review explains that GCS effectively reduced the rates of DVT in hospitalized surgical patients, whether used alone or in combination with chemical chemoprophylaxis.[37] In eight studies which compared the effectiveness of GCS with no other prophylaxis, DVT rates reduced from 26 to 12%.[37]

Recommendation

2.3.1 *In critically ill medical patients who cannot receive pharmacological VTE prophylaxis because of some contraindication, the panel recommends using mechanical method of thromboprophylaxis (IPCD or GCS).*

Strong recommendation is given by eight panelists but the remaining three panelists chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data.

In a cohort study of 798 ICU patients analyzed prospectively, it was shown that IPCD use significantly lowered the incidence of VTE, compared to no mechanical thromboprophylaxis. However, use of GCS was not associated with decreased VTE incidence. This effect was consistent irrespective of the type of heparin used for prophylaxis, history of recent surgery, or recent trauma.[38]

A recent systematic review and meta-analysis showed that use of the IPCD significantly reduces the incidence of VTE as compared to no thromboprophylaxis. Also use of the IPC showed lower incidence of VTE compared to the use of GCS.[39]

Also occurrence of pressure injuries are a significant complication of GCS noted in postsurgical ICU patients.[40]

Recommendation

2.3.2 The panel recommends using IPC devices as the choice for mechanical thromboprophylaxis for VTE. If IPC is not available, use GCS.

Strong recommendation is given by eight panelists but the remaining three panelists chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data.

2.4 Combining Different Methods of Thromboprophylaxis

A Cochrane Collaboration meta-analysis found that IPC plus pharmacologic prophylaxis reduces symptomatic PE (1.2 vs 2.9%) but not DVT (2.9 vs 6.2%) compared to pharmacologic prophylaxis alone. However, the studies included were not limited to critically ill patients.[41]

A pragmatic, randomized, multicenter trial (PREVENT Trial)[42] showed that the use of adjunctive IPCD (used for a median of 22 hours daily) along with pharmacological thromboprophylaxis did not significantly reduce the incidence of proximal lower-limb DVT as compared to use of pharmacologic thromboprophylaxis alone, in 2,003 critically ill patients. Incidence of proximal DVT was 37 of 957 patients (3.9%) in the pneumatic compression group (pharmacological + IPC) vs 41 of 985 patients (4.2%) in the control (pharmacological) group [relative risk, 0.93; 95% confidence interval (CI), 0.60–1.44; $p = 0.74$]. However, in this trial, the DVT rate was lower than expected in the control group.

Recommendation

2.4 *Panel recommends against the routine use of combined mechanical plus pharmacological prophylaxis for DVT prevention.*

Strong recommendation is agreed by all 11 panelists.

2.5 Duration of DVT Prophylaxis

The optimal degree of ambulation that provides protection or reduces the risk of DVT is unknown. Although data do not support routinely extending the duration of thromboprophylaxis in critically ill medical patients beyond admission, few selected populations may probably benefit from thromboprophylaxis for an extended duration (e.g., stroke, nonambulatory patients, patients not able to independently ambulate or patients mechanically ventilated who are admitted to acute rehabilitation unit for physical therapy or for ventilator weaning).

Three RCTs and a recent meta-analysis found nonsuperiority of extended course of thromboprophylaxis with DOACs (30–42 days of the DOAC including rivaroxaban, betrixaban, and apixaban), compared to a standard course of LMWH (7–14 days of the LMWH mainly enoxaparin) in acutely ill inpatient treatment, in terms of mortality, symptomatic DVT. However, patients on DOACs had a slightly increased risk of major bleeding.[34,35,43]

Although extended duration prophylaxis (i.e, beyond the acute hospital stay) has proven to be beneficial in some high-risk surgical patients (e.g., patients with total hip replacement), similar benefits have not been consistently observed in patients admitted for critical illnesses.[11,12]

A systematic review with 18 articles, including 7 RCTs, found no high-quality evidence supporting ambulation as a sole effective prophylaxis for VTE in hospitalized patients. Ambulation cannot be considered as an adequate prophylaxis for VTE nor as an adequate reason to discontinue pharmacologic prophylaxis for VTE during the duration of patient's hospital admission.[44]

Similar studies have not been done in the critically ill population.

Recommendation

2.5 *VTE prophylaxis should continue until the patient is discharged from the ICU.*

Strong recommendation is agreed by all 11 panelists.

2.6 Prevention of PE (post-DVT)

There is no strong evidence to prove efficacy of IVC filter in preventing VTE, and its use is controversial. They may be considered in patients with an active DVT below the level of IVC and an absolute contraindication to anticoagulants for the prevention of DVT.

Decouses H et al. did a two-by-two factorial design study in 400 patients and showed the initial beneficial effect of using vena caval filters in high-risk patients with proximal vein thrombosis was negated by an excess of recurrent DVT with no change in the mortality.[45]

Few selected patients in the very high-risk category might benefit from optional IVC filters.[46] In patients with absolute contraindications for the use of anticoagulation and a high risk of VTE recurrence, IVC filters might be tried.[46] In fact, in one study, IVC filter placement was associated with higher 30 days mortality in patients with VTE in whom anticoagulation was contraindicated.[47]

Also, an IVC filter is associated with complications which include DVT and IVC thrombosis with potential extension into the renal veins, filter fracture, strut perforation, and embolization, high cost, and rare removal (<10% of the time in a 2013 survey in trauma patients).[48]

Recommendation

2.6.1 Routine placement of endovascular (IVC) filters for prevention of thromboembolism, in patients with proximal DVT cannot be recommended.

Strong recommendation is agreed by all 11 panelists.

Meta-analysis of 13 studies including a total of 3,269 patients suggests that compared to complete bed rest, early mobilization in patients with lower extremity DVT, on anticoagulation does not elevate the risk of PE or DVT progression.[49]

The American College of Chest Physicians (ACCP) guideline recommendations for early mobilization are also based on a small number of studies and therefore subject to bias.[50] Mobilization may also be advantageous in reducing pain and edema associated with DVTs; However, larger scale studies with higher patient numbers are needed to confirm these outcomes.

Recommendation

2.6.2 *Panel encourages patients to mobilize as soon as possible post-DVT, as it may be associated with lesser complications.*

Strong recommendation is given by nine panelists but two of the panelists stated that it is plausible but due to poor literature, they gave a conditional recommendation.

B. Special Considerations

1. Catheter-related DVT—Site of Cannulation

In a multicenter randomized control trial,[51] central venous cannulation of FV was found to be associated with significantly increased incidence of catheter-related thrombosis when compared to SV (21.5% in FV vs 1.9% in SV with $p < 0.001$). FV cannulation was identified as an independent risk factor for venous thrombosis (odds ratio 14.42). Not only was there higher incidence of thrombosis in FV, it was also associated with higher incidence of complete venous thrombosis when compared to SV catheterizations (6% in FV vs 0% in SV; $p < 0.01$).[51]

In a prospective analysis, Malinoski et al. evaluated the association between the catheterization site and risk of thrombosis. Various catheter types like multi-lumen catheters, introducer sheaths, hemodialysis catheters, and peripherally inserted central catheters were assessed.[52] The authors showed that IJV cannulation resulted in a 7-fold higher risk of venous thrombosis, when compared to SV. SV cannulation had the least association with catheter related DVT (9/1,000 CVC days in SV vs 61/1,000 CVC days in IJV). After regression analysis, the authors showed that IJV cannulation was an independent predictor of catheter-related thrombosis (odds ratio 6.0 with 95% CI). IJV cannulation as a risk factor for catheter-related DVT has been confirmed in multiple other studies.[53,54]

In a Cochrane review comparing CVC insertion routes, subclavian was proved to be the preferred route instead of femoral for short term CVC insertion because of less thrombotic complications.[55]

A multicenter RCT of 3,471 catheters used in adult ICUs found lower risk of symptomatic thrombosis in the subclavian route of catheterization, as compared to the jugular and FV catheterization.[56]

Right-sided vessels are commonly used for cannulation. Critically ill patients might require catheters multiple times, necessitating multiple site cannulations. In a large observational study involving cancer patients,[57] left-sided SV cannulations were associated with a higher incidence of venous thrombosis (87.5% vs 62%), compared to the right side.

Recommendation

3.1 *Panel recommends using the SV as a preferred site for insertion for central venous catheters to prevent DVT followed by IJV. FV should be chosen as the least preferred site for the same reason. Consider all other risk factors associated with various sites for central venous cannulation before deciding about the site of cannulation.*

Strong recommendation is given by seven panelists but the remaining four chose to give a conditional recommendation due to nonavailability of adequate evidence from large clinical trials and meta-analysis.

2. Trauma

International multicenter trauma registry–based study[3] and metanalysis[1] of seven RCTs showed that DVT prophylaxis with any method is recommended in major trauma. Early chemical thromboprophylaxis within 48 hours did not significantly increase the bleeding complications, and it appears that prophylaxis decreases asymptomatic DVT but has no effect on PE and mortality. Thus, it is safe to start chemoprophylaxis early. Interestingly, most VTE occurred despite adequate prophylaxis being given.[58,59]

In acute spinal cord injury, both LMWH and UFH are safe and have lower incidence of PE. Also, pharmacological prophylaxis is better than mechanical prophylaxis. In terms of prevention of symptomatic VTE or fatal PE, there is no difference between LMWH and UFH. LMWH should be withheld on the morning of surgery and restarted within 24 hours after the surgery once stable for bleeding risk.[60–62] No difference was seen between different LMWH in prevention of DVT or bleeding risk.[63]

Studies have shown that severe TBI patients without coagulopathy, with a neurologically stable injury and with low hemorrhagic risk clinically or on repeat imaging, starting chemoprophylaxis at 24–48 hours, doesn't increase bleeding risk.[64,65] There is no strong evidence for preferred agent and dose of chemical VTE prophylaxis. Chemoprophylaxis reduces clinical VTE but no difference in PE in TBI patient.[2]

Early prophylactic IVC filter placement after major trauma is not found to reduce the incidence of symptomatic PE or death at 90 days as compared to no filter placement.[66]

In a recent multicenter, RCT, 240 severely injured patients (with an Injury Severity Score >15) who had a contraindication to the use of prophylactic anticoagulation were assigned to either placement of a vena cava filter within the first 72 hours after admission or to no filter placement. Early prophylactic vena cava filter did not result in a significantly reduced incidence of symptomatic PE or death, compared to no IVC filter placement (13.9% in the vena cava filter group and 14.4% in the control group; hazard ratio, 0.99; 95% CI, 0.51–1.94; $p = 0.98$). Early prophylactic use of an IVC filter after major trauma did not lead to a lower incidence of symptomatic PE or death at 90 days as compared to no filter placement.[67]

Recommendation

3.2 *In patients of trauma, the panel recommends the initial use of mechanical prophylaxis for DVT prevention in severe trauma (including TBI, spinal cord injury, blunt abdominal trauma). Once the risk of increase in size of hematoma/onset of fresh bleeding has been judged to be acceptable, chemical prophylaxis can be considered after 24–48 hours of ICU admission.*

Strong recommendation is given by seven panelists but the remaining four panelists chose to give a conditional recommendation as evidence from large clinical trials and meta-analysis is lacking.

3. Critically Ill Surgical Patients

In a meta-analysis of seven RCTs and one systemic review, it is observed that LMWH and UFH are effective for VTE and PE prevention in critically ill patients undergoing major surgery. Low molecular weight heparin was found to be better than UFH for decreasing PE and symptomatic PE. Incidence of major bleeding events and mortality rates were not significantly

affected by the type of heparin thromboprophylaxis in the ICU setting.[26–28]

Recommendation

3.3 *Panel recommends early use of UFH or LMWH in critically ill surgical patients. Mechanical prophylaxis should be used until the risk of bleeding is high, postsurgery.*

Strong recommendation is agreed by all 11 panelists.

4. Cardiac Surgery Patients

In one meta-analysis including observational studies ($n = 49$), RCTs ($n = 16$), and meta-analysis ($n = 3$), use of VTE prophylaxis decreased the risk of PE (patients were evaluated for clinical signs and PE was confirmed by pulmonary angiography or perfusion scan) [relative risk (RR), 0.45; 95% CI, 0.28–0.72; $p = 0.0008$] or symptomatic VTE (RR, 0.44; 95% CI, 0.28–0.71; $p = 0.0006$) without significant heterogeneity, as compared to the control.[68]

High-risk cardiac surgery patients, previous history of VTE, obesity, left or right ventricular failure, prolonged bed rest, mechanical ventilation >24 hours, use of a CVC, and blood transfusion were common factors associated with an increased VTE risk.[4,68]

There was no increased incidence of bleeding or cardiac tamponade requiring reoperation in this group of patients with the use of pharmacological VTE prophylaxis, without use of any systemic anticoagulation for other indications.

Recommendation

3.4 *Panel recommends initiating pharmacological VTE prophylaxis as quickly as feasible after high-risk cardiac surgical procedures for patients with no risk of life-threatening bleeding.*

Strong recommendation is given by eight panelists but the remaining three chose to give a conditional recommendation as clinical outcome data are insufficiently convincing.

5. Severe Sepsis[69–71]

Septic patients admitted to the ICU were found to have a 12.5% incidence of VTE in a retrospective study of 335 patients and a 37% incidence of VTE in a prospective study of 113 patients.[12,72]

Trials for VTE prophylaxis in the ICU mainly include an undifferentiated group of critically ill; thus, evidence in support of use of pharmacologic prophylaxis in septic patients is indirect. A large prospective RCT compared the incidence of VTE in septic patients who received activated drotrecogin alfa (DrotAA) (now not used). The patients were randomized to receive either placebo or UFH or LWMH. The study found that the overall safety profile was acceptable in patients with severe sepsis given DrotAA and suggested to carefully weigh the discontinuation of heparin in this group of patients.[73]

Recommendation

3.5 Patients with sepsis must receive daily chemoprophylaxis against DVT. Chemoprophylaxis includes once daily LMWH vs twice or thrice daily UFH.

Strong recommendation is agreed by all 11 panelists.

6. Renal Failure

Renal failure leads to endothelial injury/dysfunction, initial platelet hyperreactivity, increased fibrin formation, and reduced fibrinolytic system activity, thus increasing the risk of VTE. Also platelet aggregation and adhesion are reduced as a consequence of progressive renal dysfunction, thus increasing the risk of bleeding as well.[74] Hence, critically ill patients with renal insufficiency should be given individualized VTE prophylaxis in the context of the thromboembolic and hemorrhagic risks and should be closely monitored.

Low-molecular-weight heparin are more dependent on renal function for clearance than UFHs, and thus, bioaccumulation of LMWH is increased in patients with renal insufficiency, further increasing the chances of bleeding.[75]

In a retrospective, single-center, cohort study including 460 ICU patients with renal impairment, DVT prophylaxis was administered with either enoxaparin or UFH, it was found that use of enoxaparin for thromboprophylaxis in renally impaired critically ill patients, was associated with an increase in major bleeding events compared to UFH.[76]

Two small recent prospective observational studies consisting of 19 patients[77] and 138 ICU patients,[78] with an estimated creatinine clearance under 30 mL/minute, found that Dalteparin did not bioaccumulate. Dalteparin has not been shown to increase the risk of bleeding in critically ill patients with severe renal insufficiency. However, the effect of LMWHs on the bleeding risk in this group of patients other than that of Dalteparin remains controversial.

Recommendation

3.6 In patients with renal failure, prophylactic anticoagulation therapy for a short duration for DVT and VTE is recommended, and the decision to proceed to a prolonged therapeutic anticoagulation needs to be critically evaluated individually.

In critically ill patients with renal failure, especially with creatinine clearance is <30 mL/minute, use of UFH or Dalteparin or any LMWH that has a low degree of renal metabolism, should be preferred.

Strong recommendation is agreed by all 11 panelists.

7. Heart Failure[79]

Acutely ill medical patients with congestive heart failure, who are immobilised and have one or more of the following additional risk factors (active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease) should receive thromboprophylaxis with either LMWH or UFH or Fondaparinux.

Recommendation

3.7 All patients with heart failure with a low bleeding risk should receive LMWH or Fondaparinux.

Strong recommendation is given by nine panelists but the remaining two chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data.

8. Neurological Conditions

In a review of 16 trials with 23,043 patients, higher doses of UFH and LMWH decreased the risk of DVT and PE, but this benefit is counterbalanced by an increased risk of intracranial or extracranial bleeding. Standard doses of UFH and LMWH were beneficial without an increased risk of ICH.[80] Both aspirin and mechanical prophylaxis have been found to be suboptimal to prevent VTE.[81]

Trials for use of VTE prophylaxis in acute hemorrhagic stroke are limited and with a smaller sample size. Patients admitted with primary intracerebral haemorrhage and TBI should be given IPC

immediately on admission, followed by either low-dose LMWH or UFH 3–4 days after stroke onset or 24 hours after injury or surgery, respectively, and once the bleeding has stopped.[82]

In a trial, 68 patients with primary intracerebral haemorrhage were randomized to receive low-dose heparin (5,000 units three times daily) beginning on either day 2, 4, or 10 after the onset of stroke or placebo.[83] Those administered with heparin from day 2 had a significantly reduced incidence of PE, with no increase in rebleeding.

In another double-blind RCT of patients undergoing elective neurosurgery patients demonstrated that LMWH given within 24 hours after surgery along with compression stockings more effectively prevented the occurrence of VTE than use of compression stockings alone (RR 0.51; 95% CI 0.33–0.80).[84] The incidence of major bleeding events including intracranial bleeding was similar in both the groups, thus concluding that enoxaparin can be safely be administered within 24 hours after elective neurosurgery.

Recommendations

3.8.1 In case of ischemic stroke, chemical prophylaxis should be initiated for all the patients with low bleeding risk, within 24 hours of admission.

Strong recommendation is given by three panelists but the remaining eight chose to give a conditional recommendation due to absence of adequate evidence on clinical outcome data.

3.8.2 In cases of hemorrhagic stroke and neurosurgical patients, chemical prophylaxis can be considered after 24–48 hours and after clinical, radiological, and neurosurgical review.

Strong recommendation is given by three panelists but the remaining eight chose to give a conditional recommendation due to nonavailability of convincing clinical outcome data.

9. Pregnancy[85–89]

Pregnancy is a hypercoagulable state, and risk for VTE in critically ill pregnant patients is high. ACCP and American College of Obstetricians and Gynecologists recommend clinical surveillance and anticoagulant prophylaxis in the postpartum period for mothers with a single previous episode of VTE caused by a transient provoking risk factor which is no longer existing.

There are no studies regarding use of DVT prophylaxis in critically ill pregnant patients and the choice of agent. UFH and LMWH use has been found to be safe and effective in pregnancy.[90,91]

Recommendation

3.9 All critically ill pregnant patients should receive thromboprophylaxis with LMWH or UFH if the risk of bleeding is low. In those with a high bleeding risk, use of mechanical device for DVT prophylaxis should be considered.

Strong recommendation is agreed by all 11 panelists.

10. COVID-19 Disease

COVID-19 disease has been recognized as a hypercoagulable state, and several interim consensus statements recommended the use of a pharmacologic agent for thromboprophylaxis in COVID-19 hospitalized patients. Also, 3.5 times higher rates of failure of LMWH prophylaxis have been noted in patients with COVID-19.[92]

Recommendation

3.10.1 All severe and critically ill COVID-19 patients have a high risk of VTE, so use of pharmacological prophylaxis of VTE is strongly recommended in the absence of contraindications.

Strong recommendation is agreed by all 11 panelists.

3.10.2 In severe or critically ill COVID-19 patients at high risk of bleeding or with active bleeding contraindicating temporarily pharmacological thromboprophylaxis, it is recommended to use mechanical prophylaxis for VTE prevention.

Strong recommendation is agreed by all 11 panelists.

Three large international clinical trial platforms harmonized their study protocols and outcomes to study the role of therapeutic-dosed anticoagulation with heparin in critically ill patients with COVID-19. These trials consist of the ACTIV-4 (NCT04505774), REMAP-CAP (NCT02735707), and the ATTACC (NCT04372589) and are collectively called multiplatform RCT.

However, after an interim analysis and following the advice from the data and safety monitoring board, this multiplatform trial discontinued further enrolment for ICU patients on December 19, 2020, as the criteria of prespecified futility boundary for the primary end point was reached, and it was not possible to exclude the potential for harm.[93] From the data of 1,098 critically ill patients, the survival to hospital discharge and number of days free from organ support were similar in patients receiving pharmacological anticoagulation in therapeutic dose or in usual care prophylactic dose.[94] The incidence of major bleeding was 3.8% in patients on therapeutic-dose anticoagulation vs 2.3% in those on usual-care prophylactic dose of anticoagulation.[94]

INSPIRATION trial studied the efficacy and safety of intermediate-dose thromboprophylaxis with LMWH (n = 276 patients) vs the standard-dose thromboprophylaxis (n = 286 patients) and found no difference in the primary efficacy outcome (a composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days) in the intermediate-dose group [126 (45.7%) patients] and in the standard-dose prophylaxis [126 (44.1%)]. The incidence of major bleeding was seven (2.5%) events in the intermediate-dose group and four (1.4%) in the group receiving standard-dose prophylaxis.[95]

Recommendation

3.10.3 We recommend use of standard anticoagulation dose for prevention of VTE in critically ill patients with COVID-19 disease. All severe and critically ill COVID-19 patients have a high risk of VTE, so prevention of VTE is strongly recommended in absence of contraindication.

Strong recommendation is agreed by all 11 panelists.

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