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REVIEW ARTICLE

Thromboprophylaxis in Intensive Care Unit Patients

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ABSTRACT

Background: Intensive Care Unit (ICU) patients are at twice the risk of experiencing thrombosis compared to patients in regular wards. This risk is associated with prolonged immobility, sedation, and neuromuscular blockade to facilitate ventilation. The incidence ranges from 8-40%. This undoubtedly leads to poorer patient outcomes, including increased patient mortality. ICU patients require prophylaxis to prevent thrombotic events. The use of thromboprophylaxis has been shown to reduce mortality rates in these patients.

Content: Intensive Care Unit (ICU) patients are at risk of developing thrombosis, which is closely related to Virchow's triad, which consists of venous stasis, endothelial dysfunction, and hypercoagulability. Considering the high morbidity associated with thrombotic events and the low side effects of carefully administered anticoagulants, pharmacological prophylaxis should be provided to all critically ill patients without contraindications to anticoagulants. Regular monitoring is necessary when administering pharmacological prophylaxis. Compared with UFH and mechanical compression, LMWH is the preferred thromboprophylaxis for ICU patients. Generally, patients weighing 50-100 kg can be given LMWH, such as enoxaparin, at a subcutaneous dose of 40 mg per day. The discontinuation of thromboprophylaxis should consider the patient's clinical condition and drug side effects.

Summary: Thromboprophylaxis is highly necessary for Intensive Care Unit (ICU) patients. The preferred thromboprophylaxis for ICU patients is LMWH. In certain circumstances, UFH or mechanical thromboprophylaxis may be considered.

Keywords: Intensive care unit; Thrombosis; Thromboprophylaxis.

INTRODUCTION

Patients in hospitals are at risk of experiencing thrombotic events. This risk increases in critical patients, especially Intensive Care Unit (ICU) patients, who have various complex comorbidities and long-term bed rest. These patients are at risk of developing venous stasis (due to bed rest) and endothelial dysfunction (due to associated comorbidities). This can trigger thrombosis, where deep vein thrombosis (DVT) and pulmonary embolism (PE) are conditions that can arise. DVT and PE are complications that often occur in critical patients, especially ICU patients. The risk of ICU patients developing VTE is 2 times greater than that of patients in ordinary wards[1]. This increased risk for ICU patients is associated with prolonged immobility, sedation, and neuromuscular blockade to facilitate ventilation[2]. The independent risk factors for DVT are older age and longer length of stay in the ICU[3]. Research by Cook et al. (2005) showed that the incidence of DVT upon admission to the ICU can reach 10% and that the incidence of DVT developing during the ICU stays ranges from 8% to 40%[4]. A meta-analysis revealed that patients with DVT had longer ICU and hospital stays than did those without DVT (11.2 days; 95% CI: 3.82–18.63 days; and 7.28 days; 95% CI: 1.4–13.15). Patients with DVT have a significantly increased risk of in-hospital death (RR 1.31; 95% CI: 0.99–1.74; p=0.06) (5). Patients in the ICU often suffer from septic shock. This, in turn, can also trigger thrombotic events. The incidence rate of venous thromboembolism (VTE) in patients with sepsis and septic shock is 37.2%[6].

Intensive Care Unit patients require prophylaxis to prevent thrombotic events. Ejaz et al. (2018) reported that thromboprophylaxis can reduce the death rate in these patients[7]. A randomized controlled trial (RCT) concluded that the incidence of DVT in patients admitted to the ICU was significantly lower in patients receiving thromboprophylaxis[8–10]. However, it is important to remember that this prophylaxis has the main side effect, namely, bleeding. In fact, ICU patients are at risk of experiencing severe bleeding[11]. Therefore, it is also necessary to consider the side effects of this bleeding. Therefore, it is important to provide a reference regarding thromboprophylaxis for patients in the

ICU. With this recommendation, it is hoped that the management of thromboprophylaxis for critical patients can lead to better outcomes.

Physiology of Trombosis

Blood is an important component of the human body, and one of its tasks is to transport oxygen to tissues. Under severe conditions, blood loss can be life threatening. The human body protects itself from blood loss through the clotting mechanism. This clotting mechanism involves several factors, such as platelets, blood vessels, prostaglandins, clotting factors, prostaglandins, proteins and enzymes, that form clots together to stop bleeding. Through the phases of activation, adhesion, vasoconstriction and aggregation, these factors form a temporary blockage to stop blood vessel leakage. After that, the fibrinogen becomes fibrin and stabilizes this weak platelet blockage. The body's clotting mechanism is ultimately divided into 2 phases: primary and secondary hemostasis[12].

Primary hemostasis

Primary hemostasis is the process of blocking weak platelets and occurs in four phases: vasoconstriction, adhesion, activation, and platelet aggregation. Vasoconstriction is the initial response when an injury occurs to a blood vessel. Endothelin-1 is the main vasoconstrictor mediator produced by damaged endothelium. Damaged endothelium releases von Willebrand factor (vWF), subendothelial collagen, ATP and inflammatory mediators. vWF is produced by megakaryocytes and is then stored in platelets on alpha granules. After this process, the second phase of primary hemostasis, namely, platelet adhesion, occurs[12.]

Platelet adhesion is the process by which platelets adhere to subendothelial-bound vWF. After damage to a blood vessel, platelets begin to roll along the vessel wall and adhere to subendothelial collagen and vWF areas on the endothelium. Platelet membranes are rich in G protein (Gp) receptors located in the phospholipid bilayer. Specifically, the Gp Ib-IX receptor on platelets binds to vWF on the endothelium, linking the two factors. The third phase of primary hemostasis initiates platelet activation after the bond is successfully formed[12]. After platelets attach to vWF in the endothelium, the platelet activation process occurs. Platelet activation via two mechanisms is mediated by

thrombin. In the first mechanism, thrombin activates platelets directly through breaking proteolytic bonds by binding to protease receptors. In addition, thrombin also initiates the release of platelet granules, including platelet activating factor, adenosine diphosphate (ADP) and serotonin. ADP is a physiologically important agonist that is specifically stored in dense platelet granules. ADP will bind to the P2Y1 and P2Y12 receptors on the platelet membrane when released. The P2Y1 receptor helps platelet aggregation and stimulates changes in pseudopod shape. Moreover, the P2Y12 receptor plays an important role in triggering the blood clotting cascade. ADP induces the expression of the Gp IIb/IIIa complex on the surface of the platelet membrane when it binds to its receptor. The Gp IIb/IIIa complex is required for platelet adhesion to the endothelium and platelet aggregation with other platelets. At the same time, platelets synthesize thromboxane A2 (TXA2), which in turn causes increased vasoconstriction and platelet aggregation[12].

The platelet aggregation process begins once the platelets are activated. Once activated, the Gp IIb/IIIa receptor binds to vWF and fibrinogen. Fibrinogen in the blood circulation forms a connection between Gp IIb/IIIa receptors and platelets. The bond between Gp IIb/IIIa and fibrinogen will form a weak platelet plug. Primary hemostasis functions to form a weak platelet plug, which is the initial response when bleeding occurs until stabilization of fibrinogen into fibrin via thrombin occurs in secondary hemostasis[12].

Secondary Hemostasis

The process of secondary hemostasis occurs due to clotting factors working in a cascade to stabilize the weakened platelet plug. Secondary hemostasis can occur through two pathways, namely, the extrinsic pathway and the intrinsic pathway, where the two pathways meet each other through a common pathway after activation of factor X. Calcium is a substance that is necessary for the entire secondary hemostasis process. The extrinsic pathway involves tissue factor (TF) and factor VII (FVII). This pathway results in the formation of a TF-FVIIa complex, which begins when TF binds to FVII and activates FVII to generate factor VIIa (FVIIa). After that, the TF-FVIIa complex, which is formed, activates factor X (FX). In addition, the TF-FVIIa complex can

activate factor IX via an intrinsic pathway called the alternative pathway[12].

The intrinsic pathway involves the Hageman factor (FXII), factor XI (FXI), factor IX (FIX), and factor VIII (FVIII). This process begins when FXII interacts with exposed subendothelial collagen and becomes activated to become FXIIa. Next, FXIIa activates FXI to become FXIa, and FXIa activates FIX to become FIXa. FIXa cooperates with activated factor VIII (FVIIIa) to activate factor X. The common pathway begins through the activation of factor Xa. This thrombin activation occurs through breaking the serine protease bond with prothrombin. This causes thrombin to activate factor XIIIa (FXIIIa). After that, Factor XIIIa will cross-link with fibrin to form a stable clot[12].

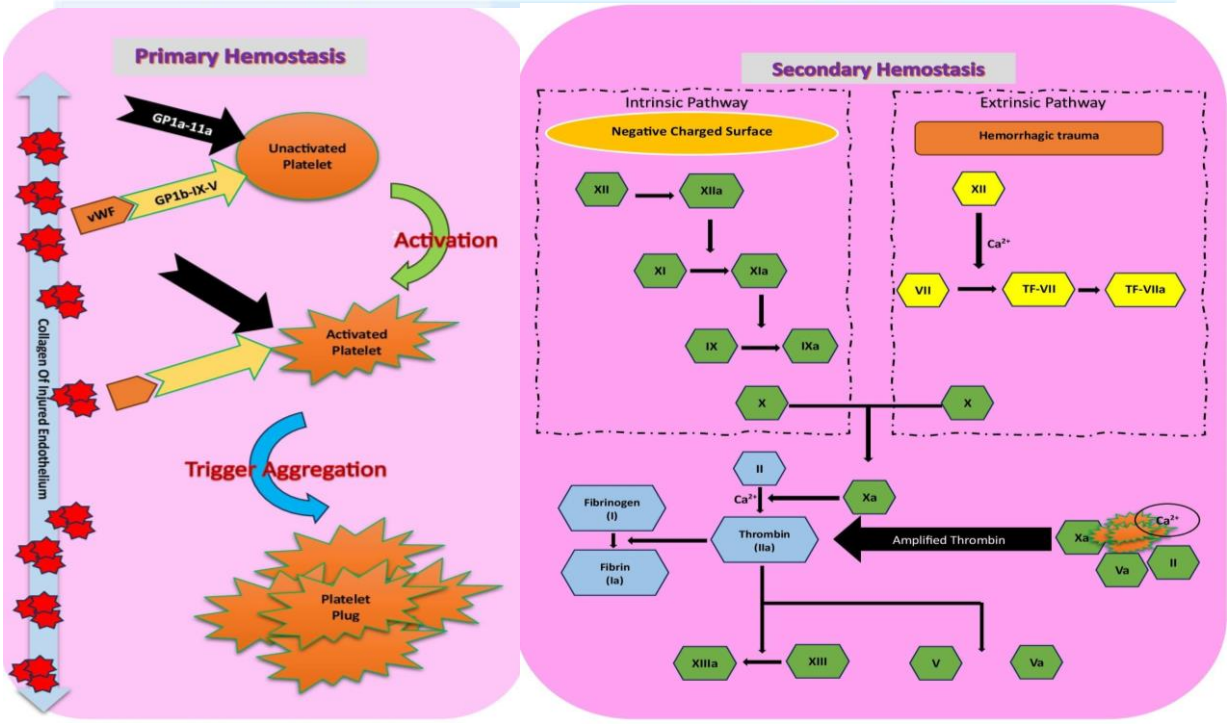

Figure 1. Primary and secondary hemostasis.[13]

Patofisiologi Trombosis

Thrombosis is the process by which clots form in blood vessels. Virchow's triad is an important concept that can cause blood clots to develop into thrombosis. The concept of thrombosis was first introduced by Virchow in 1856 with the proposal of a pathophysiological description known as Virchow's Triad, namely, stasis, activation of blood coagulation, and blood vessel damage. These three

factors play important roles in the pathophysiology of thrombosis. At least 2 factors are needed for VTE to occur. Three groups of contributing factors known as Virchow's triad are commonly found[12]:

1. Static blowflow
   Static blood flow is a predisposing factor for thrombosis and appears to be a contributing factor to immobility or conditions where limbs cannot be used for long periods of time. Immobilization, such as during the perioperative period or paralysis, eliminates the influence of peripheral venous pumps, increasing blood stagnation and pooling in the lower extremities. Blood stasis in the lower extremities predisposes patients to platelet and fibrin deposition, which triggers the development of deep vein thrombosis.
2. Endothelial injury
   Although endothelial injury is known to initiate thrombus formation, obvious lesions cannot always be detected but may be due to subtle endothelial changes caused by chemical changes, ischemia, anoxia or inflammation. An obvious cause of endothelial damage is direct trauma to blood vessels, such as that caused by chemotherapy or high doses of antibiotics.
3. Blood hypercogulability
   It depends on complex interactions between a wide variety of variables, including the vascular endothelium, clotting factors and platelets, composition and blood flow properties. In addition, the intrinsic fibrinolytic system balances the clotting system through clot lysis and dissolution to maintain vascular patency. A hypercoagulable state occurs when there is a change in any of these variables.

Normally, blood flow is laminar. Abnormal blood flow, namely, stasis or turbulent flow, causes thrombosis. Turbulent blood flow causes endothelial damage and promotes thrombus formation. Hypercoagulability (thrombophilia) is a blood disorder that increases a person’s susceptibility to thrombosis. This can occur due to inherited blood clotting disorders such as the Factor V Leiden mutation or acquired blood clotting disorders such as disseminated

intravascular coagulation (DIC). Abnormal blood flow, such as venous stasis, causes endothelial damage and triggers thrombosis. Venous stasis can occur in patients who are bedridden for a long time, such as in ICU patients. Endothelial damage initiates platelet activation and thrombus formation. This occurs due to inflammation on the endothelial surface[12].

In ICU patients, blood flow stasis plays a major role due to the inability to move due to trauma, sedative use, and neuromuscular blocks that significantly decrease the velocity of venous blood flow in the limbs. In addition, mechanical ventilation and abdominal compression, which frequently occur in many situations, reduce venous blood return to the heart and may worsen venous blood stasis in the lower leg veins. Vascular injuries are mainly caused by catheter placement in central and peripheral veins and/or surgical intervention. Finally, hypercoagulability can be caused by sepsis, renal failure, or hemodynamic disturbances resulting from the administration of vasoconstrictor drugs[14].

Thromboprophylaxis indications

Overall, critically ill patients are at high risk of VTE, which can occur despite receiving effective prophylaxis. VTE in critically ill patients is associated with unfavorable outcomes. Lilly et al. (2014) conducted an observational study on ICU patients involving 294,896 critically ill patients and reported that patients who received prophylactic anticoagulation had a significantly lower risk of death than those who were not given VTE prophylaxis[15]. For this reason, considering the many benefits of this prophylaxis, Boonyawat & Crowther (2015) reported that pharmacological prophylaxis for VTE should be applied to all critical patients who do not have contraindications for anticoagulants[16].

Guidelines from NICE (2018) recommend that all patients aged 16 years and older admitted to the ICU undergo a VTE risk assessment and bleeding risk review within 24 hours of ICU admission[17]. However, Boddi & Peris (2016) reported that the risk assessment model for the diagnosis of DVT used for outpatients (Wells score), inpatients (Padua score), surgeons (modified Caprini score) or trauma patients cannot be fully applied to critical patients[14]. These patients also

need other considerations, such as previous DVT risk factors. If thromboprophylaxis is necessary, administration must be carried out within 14 hours of ICU admission[17]. The risk of VTE and bleeding for people in the ICU should be reassessed daily or more frequently if the patient's condition changes rapidly.

Thromboprophylaxis contraindications

Contraindications for medical thromboprophylaxis include coagulopathy with an INR > 2.0 (or an INR > 2.5 in patients with chronic liver disease), a platelet count < 75 x 109/L (or a platelet count < 50 x 109/L in patients with chronic liver disease or liver transplantation), active bleeding, ischemic or hemorrhagic stroke, traumatic brain injury <72 hours, and a history of gastrointestinal bleeding in the near future (for the last 3 months). On the other hand, contraindications to mechanical thromboprophylaxis include severe arteriosclerosis or other ischemic vascular disease, severe congestive heart failure, acute DVT, thrombophlebitis, or PE[17].

Thromboprophylaxis scoring

Over the past decade, several quantitative models for VTE risk assessment (RAM) have been developed for hospitalized patients. The most studied are the Padua score and the IMPROVE score. Both have been externally validated and shown to identify medical inpatients at high risk for VTE. IMPROVE researchers also developed an externally validated bleeding risk RAM[18].

Table 1. Padua score for VTE risk assessment[18].

Criteria	Score
Reduced mobility	3
Active cancer	3
Previous history of VTE	3
Thrombophilic conditions	3
Acute trauma and/or surgery (<1 month)	2
Elderly (i.e., >70 years)	1
Heart failure and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Continuous hormonal therapy	1
Obesity (body mass index >30)	1
Acute infections and/or rheumatological disorders	1

Patients with a score of 0-3 had a VTE incidence of 0.3%, while patients with a score of >4 had a VTE incidence of 11%. Giving prophylaxis to patients with a score >4 can reduce the prevalence rate to 2.2%. Considering that the benefits of reducing the incidence of VTE are greater than the risk of bleeding, prophylaxis can be given to patients with a Padua score >2[18].

Table 2. IMPROVE score for VTE risk assessment[18].

Criteria	Score
Previous history of VTE	3
Known history of thrombophilia	2
Lower extremity paralysis	2
Active cancer	2
Immobilization ≥ 7 days	1
Dirawat di ICCU/ICU selama 1 hari	1
Age > 60 years	1

According to the IMPROVE score, the percentages of patients who experienced VTE with symptoms within 3 months were as follows: IMPROVE score 0-1: 0.5%, IMPROVE score 2-3: 1.5% and IMPROVE score ≥ 4: 5.7%[18]

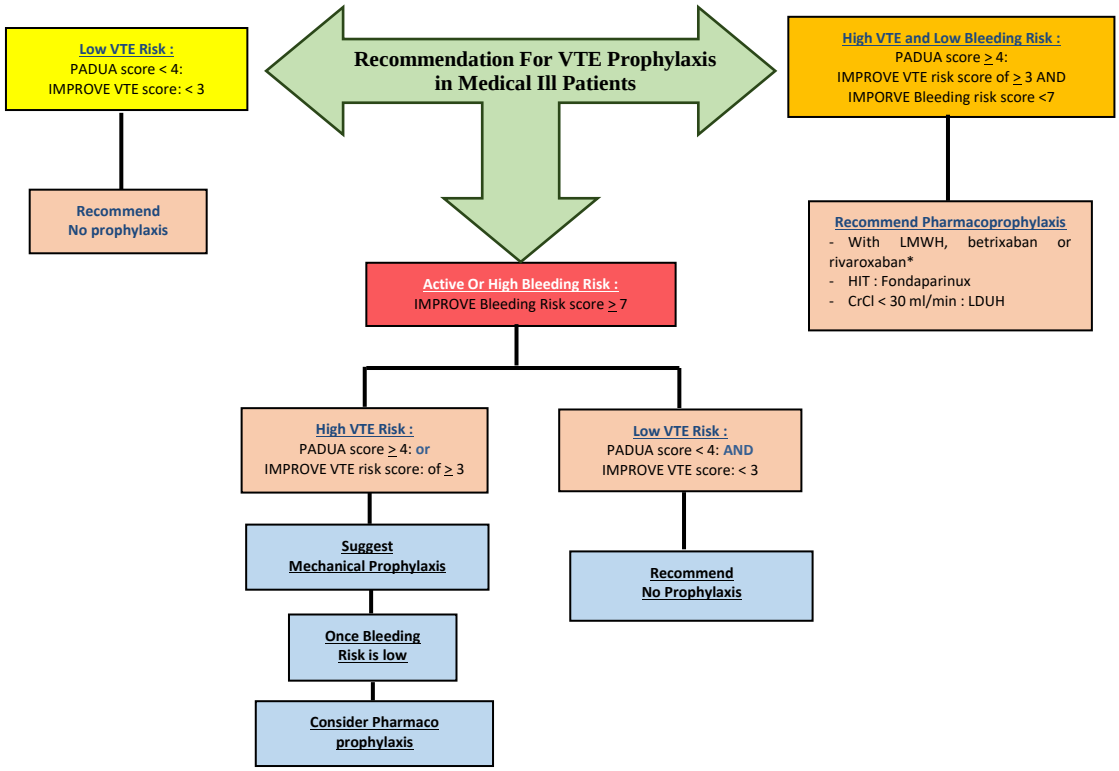

Figure 2. Recommendations for VTE prophylaxis in ICU patients[17]

Drug choices for thromboprophylaxis

The largest trial to date evaluating VTE prophylaxis in critically ill patients is the Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT). This RCT enrolled 3764 patients who received UFH compared with LMWH for VTE prophylaxis in the ICU. The study did not include patients at high risk of bleeding. The patients were randomly divided into two different groups: the first group received subcutaneous dalteparin 5,000 IU once daily plus placebo once daily, and the second group received subcutaneous UFH 5,000 IU twice daily. According to the results of this study, no significant difference was found in the incidence of proximal DVT (5.1% vs 5.8%, p=0.57). However, the incidence of pulmonary embolism was significantly lower in the dalteparin group (1.3%) than in the UFH group (2.3%) (p=0.01). A systematic review with meta-analysis by Beitland et al. (2015), involving ICU patients with trauma, showed that LMWH, compared with UFH, reduced the risk of DVT (RR 0.84, 95% CI 0.71-0.98), p = 0.03) (19). There were no statistically significant differences in the risk of developing PE, major bleeding, or death.

The NICE guidelines (2018) recommend the use of low molecular weight heparin (LMWH) for all patients admitted to the ICU unless there is a contraindication[17].

However, considering that the clearance of UFH is independent of renal function, this is an advantage over LMWH[16]. Most critically ill patients have impaired renal function, which may limit the use of LMWH. However, LMWH may be preferred in critically ill patients if it is proven to have better efficacy and because it has a lower probability of causing HIT, as well as requiring once-daily administration and being available in unit doses, which reduces the possibility of medication errors[21].

In addition, the relative risk of thrombosis versus the risk of bleeding should always be considered. All critical patients will receive mechanical VTE prophylaxis, such as intermittent pneumatic compression (IPC). This should be initiated upon admission to the ICU unless there is a contraindication to its use. Each patient should be reassessed daily until they no longer have limited mobility compared

to normal or expected mobility. If there are no contraindications, all patients will receive mechanical and pharmacological thrombosis prophylaxis. Nicolaides et al. (2013) recommend the use of LMWH (dalteparin) (level of evidence: high). For patients with contraindications to pharmacological prophylaxis, the use of graduated elastic compression stockings with IPC is an alternative (level of evidence: low). If there are no contraindications, we recommend a combination of mechanical and pharmacological prophylaxis (level of evidence : low)[22].

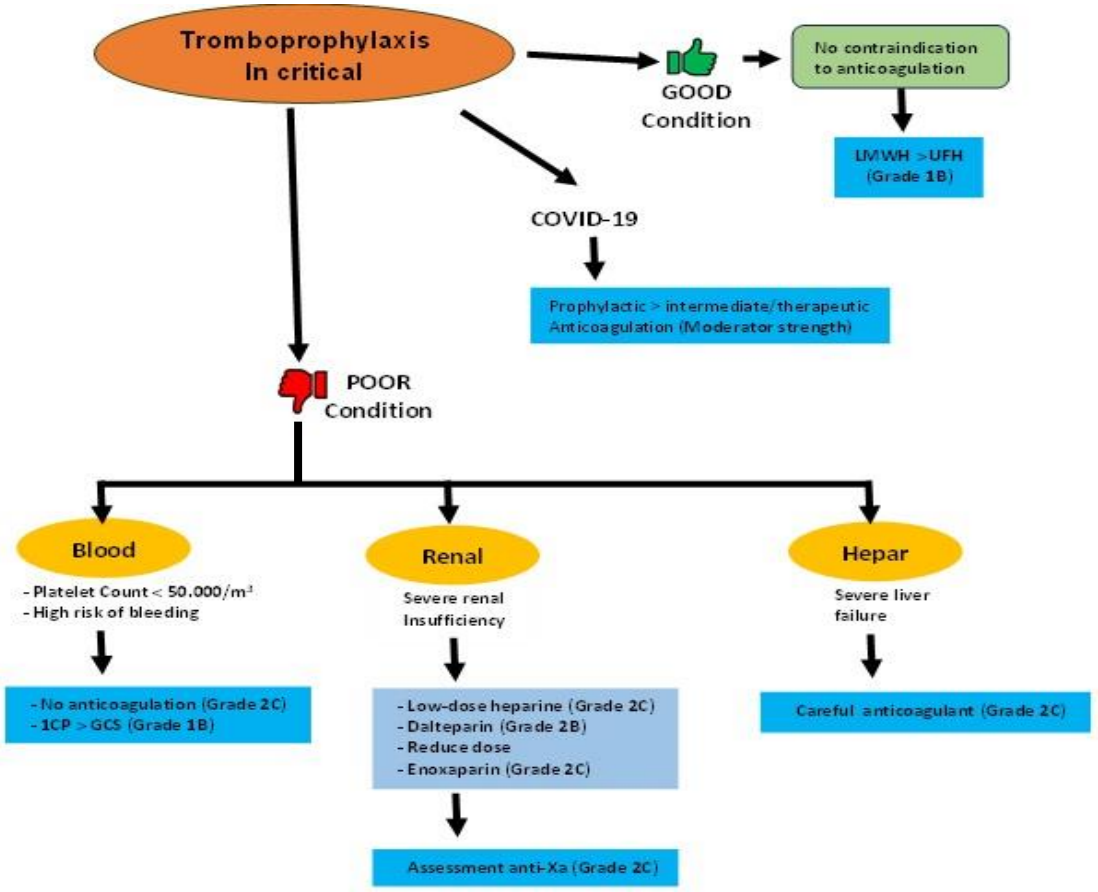

Figure 3. Algorithm for administering thromboprophylaxis to critical patients[22]

Clinical guidelines from the American Society of Hematology (2018) have provided several recommendations regarding VTE prophylactic management in critical patients[18]:

- In critical patients, the use of UFH or LMWH is recommended over no use of UFH or LMWH (strong recommendation, moderate evidence).

- In critical patients, the use of LMWH is recommended over UFH (conditional recommendation, moderate evidence).
- In critical patients, the use of medical VTE prophylaxis is recommended over mechanical VTE prophylaxis (conditional recommendation, very low evidence).
- In critically ill patients not receiving pharmacologic VTE prophylaxis, the use of mechanical VTE prophylaxis is recommended over no VTE prophylaxis at all (conditional recommendation, moderate evidence).
- In critical patients, pharmacological or mechanical VTE prophylaxis alone is preferred over mechanical VTE prophylaxis combined with pharmacological treatment (conditional recommendation, very low evidence).
- In critically ill patients receiving mechanical VTE prophylaxis, the use of pneumatic compression devices or graduated compression stockings for VTE prophylaxis is recommended (conditional recommendation, very low evidence).
- In critically ill patients, VTE prophylaxis during hospitalization is recommended rather than a combination of inpatient and outpatient treatment of extended duration (strong recommendation, moderate evidence).

Currently, novel anticoagulants, which are direct inhibitors of thrombin or factor Xa, are available for primary and secondary prevention of DVT. None of these new anticoagulants have been studied in an ICU population, and results from the MAGELLAN trial, rivaroxaban vs. enoxaparin, and the ADOPT trial, apixaban vs. enoxaparin, conducted in acute illness, cannot be directly generalized to the ICU setting (23,24). Currently, the lack of data regarding the effectiveness and safety of NAO in the ICU setting, as well as the lack of an antidote to control bleeding, are reasons not to use NAO in critical patients[14].

Table 3. Several tests have demonstrated thromboprophylaxis in the ICU[16].

Author	Patient	Intervention	Incidence of DVT (%)	Sig.
Zhang Ran et al (25)	4950 medical-surgical ICU	Low molecular weight heparin (LMWH)	15.8	<0.05
Wang Lu et al (26)	200 medical ICU	Heparin vs. mechanical devices	10	0.02
Alhazzani Waleed (27)	223 mechanically ventilated COPD	LMWH vs. unfractionated heparin (UFH)	7,2	<0,01
Hui Jiang (28)	2000 medical icu	UFH vs. LMWH	6,9	0,04
		LMWH vs. UFH		
Fowler et al (29)	3746 ICU patient	LMWH 5000 IU daily (Dalteparin) vs UFH 5000IU bid	5,1 vs. 5,8	p=0,57
Jacobs et al (30)	18010 medical ICU	LMWH 40 mg daily vs. UFH 5000IU bid	NS	P=0,01
Samuel et al (31)	2228 patient ICU	LMWH (enoxaparin) 40 mg sc bid vs. UFH 5,000 units sc bid	NS	0,089
Wadhera et al (32)	1862 patient ICU	LMWH 40 mg daily vs. UFH 5000IU bid	NS	P<0,05

Thromboprophylactic dosage

In principle, the dose of LMWH should be adjusted according to the actual body weight, renal function, and use of renal replacement therapy[17]. The standard treatment for high-risk patients weighing 50 - 100 kg is subcutaneous injection of 40 mg enoxaparin daily. The following is a table of enoxaparin dosages for patients[33]:

Table 4. The enoxaparin dosage for patients with creatinine clearance was greater than 30 mL/minute[33]

Weight	Enoxaparin Dosage
<50 kg	20 mg per day
50 – 100 kg	40 mg per day
101 – 150 kg	40 mg twice daily
150 kg	60 mg twice daily

Table 5. The enoxaparin dosage for patients with creatinine clearance was less than 30 mL/minute[33]

Weight	Dosis Enoxaparin
<50 kg	20 mg once daily taking into account factor Xa
50 – 100 kg	20 mg once daily
101 – 150 kg	40 mg per day
>150 kg	60 mg per day

Mechanical Thromboprophylaxis

Mechanical thromboprophylaxis may be considered using graded compression stockings (GCS) or intermittent pneumatic compression (IPC) if the patient has contraindications to anticoagulant medications [(7,34)]. IPC use was associated with a significantly lower risk of VTE (35). On the other hand, the GCS is at high risk of pressure injuries in surgical ICU patients[36].

TED/Thromboembolism

Deterrent stockings (GCS) are designed to create 18 mmHg of external pressure at the ankle and 8 mmHg of external pressure at the thigh. A pressure difference of 10 mm Hg produces a pressure gradient that acts as a driving motor for venous outflow from the legs. These stockings have been shown to reduce the incidence of VTE when used alone after abdominal surgery and neurosurgery. However, this method is considered the least effective for thromboprophylaxis and is almost never used alone in patients at moderate or high risk of VTE.

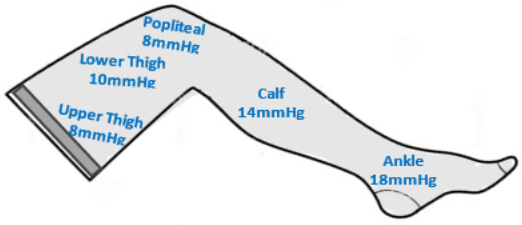

Figure 4. Graded Compression Stockings[36].

The Intermittent Pneumatic Compression (IPC) pump is an expandable sac that is wrapped around the lower leg. When inflated, the device creates 35 mm Hg of external compression at the ankle and 20 mm Hg

of external compression at the thigh. The device also creates a pumping action that periodically inflates and deflates, and this action further increases venous flow[35].

Intermittent Pneumatic Compression is considered more effective than GCS for thromboprophylaxis, and this method can be used alone for selected patients who are not suitable for anticoagulant prophylaxis because of bleeding. This method is very popular after intracranial surgery and for trauma victims who are at risk for bleeding. Apart from the above mechanical methods, early mobilization can also improve venous blood flow to avoid venous blood flow stasis[35].

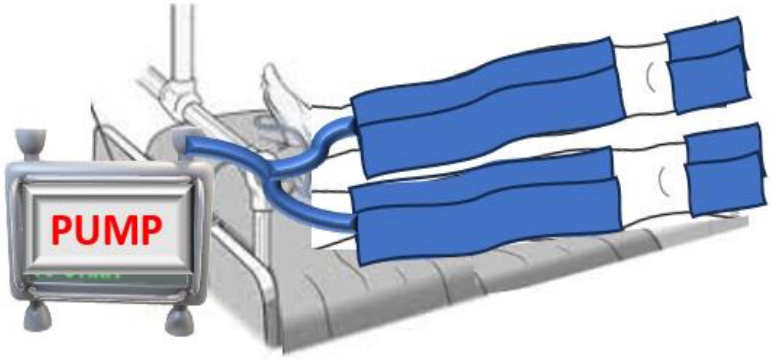

Figure 5. Intermittent Pneumatic Compression (IPC) Pump[35]

Discontinuation of thromboprophylaxis

Until now, there has been no information in the literature about when thromboprophylaxis should be stopped in ICU patients. In principle, if there are side effects related to thromboprophylaxis, such as bleeding events, thromboprophylaxis can be considered to be discontinued. Ejaz et al. (2018) reported that heparin administration should be temporarily stopped in patients with active bleeding or severe thrombocytopenia (<50,000/cc)[7]. However, both bleeding and the accompanying discontinuation of thromboprophylaxis are associated with poor outcomes[7].

The American Society of Hematology (2018) recommends that, in critical patients, VTE prophylaxis during hospitalization rather than a combination of inpatient and outpatient treatment of extended duration is recommended[18]. Meskipun Demikian, umumnya, diperlukan waktu sekitar 3

bulan untuk menyelesaikan pengobatan aktif VTE, dengan pengobatan lanjutan yang bertujuan untuk mencegah episode baru trombosis[37]. The decision to discontinue anticoagulant use in ICU patients or continue treatment may be based on the long-term risk of recurrence and influenced secondarily by bleeding risk and patient preference.

Thromboprophylaxis Antidote

Unfractioned Heparin (UFH)

Unfractionated heparin (UFH) does not require an antidote in most cases of bleeding because it has a short half-life. Antheparin therapy (protamine sulfate), transfusion therapy and supportive care are treatments used to treat bleeding due to UFH administration. The time of last UFH administration determines the protamine dose. For immediate antidote (last administration of UFH <30 minutes), a protamine dose of 1 mg for every 100 U of UFH can be given. When administering UFH via continuous IV infusion, only UFH administered during the previous 2-2.5 hours should be included in the calculation to determine the protamine dose. If the UFH dose is unknown, a protamine dose of 50 mg can be given slowly over 10 minutes, followed by serial aPTT assessments[38].

Unfractioned Heparin can be given IV or SC. Once administered, UFH binds to several proteins. Among the proteins bound by UFH, antithrombin is the most important protein. UFH will cause inactivation of thrombin. Binding to antithrombin blocks several factors of the blood clotting cascade, primarily thrombin and factor Xa. By inactivating thrombin, the conversion of fibrinogen to fibrin is inhibited, thereby preventing clot formation and extending blood clotting time[38]. The dose administered via the SC route must be large enough (>30,000 U/day) to overcome the low bioavailability of UFH. The anticoagulant response to UFH administration is monitored using activated partial thromboplastin time (aPTT). The aPTT was measured every 6 hours by intravenous (IV) administration, and the UFH dose was adjusted for each measurement. The frequency of monitoring can be increased if the patient is more stable[38].

The use of Unfractioned Heparin has decreased with the advent of LMWH and fondaparinux[39]. However, UFH remains the main choice for patients at risk of bleeding or critical patients with organ dysfunction.

Patients with creatinine clearance less than 30 mL/minute or fluctuating renal function are not candidates for LMWH or fondaparinux due to the risk of accumulation and an increased risk of bleeding[40]. A study by King et al. (2007) revealed that when UFH was used for thromboprophylaxis in medical patients, three daily administrations were more effective at preventing VTE events than two daily administrations but caused more bleeding episodes. The main complications of UFH therapy include bleeding and heparin-induced thrombocytopenia (HIT)[38].

Low Molecular Weight Heparin (LMWH)

Protamine can be given intravenously if an overdose or life-threatening bleeding occurs due to anticoagulant administration. Protamine cannot completely eliminate the effects of LMWH but can neutralize the effects of AT. If immediate discontinuation is required within 8 hours after administering LMWH, protamine can be given at a dose of 1 mg to neutralize 100 U of anti-Xa or 1 mg of LMWH. A second dose of protamine of 0.5 mg per 100 U of anti-Xa can be given if bleeding continues. If the interval between LMWH administration exceeds 8 hours, a smaller dose of protamine can be given[38].

Low Molecular Weight Heparin is a small fragment of heparin. The mechanism of action of UFH and LMWH is almost the same; the difference is that UFH has a faster onset of anticoagulant action because it inhibits Xa and thrombin, while LMWH only works by inhibiting Xa[41]. Compared with UFH, LMWH has better bioavailability when administered subcutaneously (SC) and has a longer half-life (17-21 hours) (42,43). Anti-Xa antibodies are commonly used to monitor LMWH use. LMWH monitoring is carried out especially in patients at high risk, such as patients with kidney failure, obesity and pregnancy. In patients at high risk, dose adjustment is needed. Anti-Xa plasma is taken 4 hours after the administration of LMWH, especially in high-risk patients. LMWH agents are preferred over UFH in patients requiring parenteral VTE prophylaxis. LMWH has fewer side effects and requires fewer injections. Administration of LMWH was associated with a lower risk of DVT and no difference in bleeding compared with UFH in ICU patients receiving thromboprophylaxis[44]. Bleeding is the

main complication of LMWH. However, the incidence of bleeding in LMWH is lower than that in UFH[38].

Fondaparinux

The antidote for fondaparinux is more difficult due to its longer half-life[45]. Although there is no specific antidote for fondaparinux-related bleeding, the administration of recombinant activated factor VII (rFVIIa) can increase coagulation time and thrombin formation[46].

Heparin can bind AT, which contains a series of active pentasaccharides. Heparin can provide a sustained anticoagulant effect by separating and binding other ATs after binding and activating ATs. Fondaparinux is a synthetic analog of the pentasaccharide heparin[39]. Fondaparinux binds selectively and irreversibly to AT. This neutralizes factor Xa, which ultimately inhibits thrombin formation and blood clot development. Fondaparinux is rapidly absorbed, with a half-life of 17-21 hours in patients with normal renal function when it is injected via the SC[39]. Fondaparinux has been shown to be as safe and effective in the treatment of DVT and PE as the LMWH and UFH agents[47]. Fondaparinux is not metabolized in the liver and is almost completely excreted unchanged in the urine by the kidneys. Therefore, fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 mL/minute)[48]. In patients weighing less than 50 kg, it is also a contraindication to administer fondaparinux as VTE prophylaxis[38].

Vitamin K Antagonists

Discontinuation of the drug is necessary to reverse the anticoagulant effects of warfarin. The duration of the effects of warfarin can last up to several days without the administration of an antidote. The administration of vitamin K is essential for reversing the anticoagulant effects of VKA in patients with clinically significant bleeding. In patients with an INR of 4.5-10 without significant bleeding, warfarin administration should be postponed, and the INR should be evaluated (49). The administration of warfarin must be stopped if serious, potentially life-threatening bleeding occurs at any INR level, and it is recommended to administer vitamin K via slow intravenous infusion of 10 mg. High doses of vitamin K have proven effective but can cause VKA resistance

for more than one week. Vitamin K can be administered orally or parenterally, with the intravenous route having a quicker response. Administration via the intramuscular or subcutaneous route is not recommended for critically ill patients because of unpredictable absorption. In patients with difficult-to-control bleeding and high INR, recombinant factor VIIa can be given[38].

Vitamin K antagonists (VKAs) have an anticoagulant effect by inhibiting vitamin K epoxy reductase, thereby inhibiting the conversion of vitamin K to vitamin KH2 (the active form of vitamin K). Clotting factors II, VII, IX, and X are factors that require γ-carboxylation of vitamin KH2 for their biological activity[50]. An example of a VKA is warfarin. Warfarin has been shown to be effective in preventing primary and secondary VTE. The main problem in warfarin therapy is bleeding due to the narrow range of available warfarin therapy. Treatment with VKAs such as warfarin increases the risk of intracranial hemorrhage by approximately 0.2% per year and major bleeding by 0.3-0.5% per year compared with the control group[38]. Risk factors for bleeding due to VKA therapy include the intensity of the anticoagulant effect, patient characteristics and duration of therapy. An INR >3 is directly related to an increased risk of bleeding[50].

Novel Oral Anticoagulant (NOACs)

Currently, there is no antidote to reverse the effects of oral anticoagulants such as dabigatran, rivaroxaban, or apixaban. If an overdose of anticoagulants occurs, activated charcoal is recommended[51]. To reverse the excessive effects of anticoagulants, it is sufficient to discontinue the drug because of its short half-life. New oral anticoagulants (NOACs), such as dabigatran, rivaroxaban and apixaban, have various advantages over previous oral anticoagulants. NOACs have a rapid onset and a more predictable response, so monitoring is easier. This drug has a lower rate of thrombosis, bleeding and side effects than LMWH or warfarin [38].

Dabigatran is excreted through renal filtration, so the average half-life of dabigatran is prolonged in patients with severe renal dysfunction. There is no antidote available to reduce or reverse the effects of anticoagulants such as dabigatran[52]. Moreover, rivaroxaban is an oral, direct, and competitive selective inhibitor of factor Xa[53]. Inhibition of factor Xa disrupts

the intrinsic and extrinsic clotting pathways, thereby preventing the formation of thrombin and subsequent blood clotting. Rivaroxaban has a different mechanism of action than LMWH or fondaparinux by inhibiting free and fibrin-bound factor Xa. The dabigatran dose should be reduced to 75 mg twice daily in patients with a creatinine clearance of 15-30 mL/minute. In patients with creatinine clearance less than 15 mL/minute, rivaroxaban is not recommended. The use of rivaroxaban does not significantly interfere with platelet function[38].

Table 6. Selection of Thromboprophylactic Agents under Special Conditions[54].

Anticoagulant Drugs	Dose	Special Conditions
UFH	5000 U s.c 2-3x/day	Impaired renal function: dose modification
LMWH	40 mg s.c. 1x/day	Impaired renal function: dose modification
Enoxaparin	5000 U s.c 1x/day	Impaired renal function: dose modification
Dalteparin	5000 U s.c 1x/day	Impaired renal function: no dose modification
Fondaparinux	2,5 mg sc 1x/day	Contraindicated in patients with impaired renal function, but may be considered in patients with impaired liver function
Rivaroxaban	20 mg PO 1x/day	Avoid in patients with impaired renal function

Pharmacokinetics and Pharmacodynamics

The coagulation cascade is triggered by the release of TF due to tissue trauma or vascular injury. TF forms a complex with factor VIIa in the presence of calcium and cleaves coagulation factors X and IX into their activated forms (factors Xa and IXa). The prothrombinase complex then forms on the phospholipid membrane and breaks down prothrombin (factor II) into factor IIa (thrombin). Thrombin is one of the most powerful activators of primary (mediated by platelets) and secondary (mediated by coagulation factors) hemostasis. Thrombin can also enhance clot formation through fibrin polymerization, platelet receptor activation, endothelial activation, and the activation of factors V, VIII, XI, and XIII. Anticoagulant agents can inhibit thrombogenesis by altering various pathways in the coagulation cascade or

by directly targeting thrombin, reducing thrombin production. Moreover, indirect inhibitors bind to plasma cofactors, such as antithrombin (AT), which can facilitate their interaction with clotting enzymes[55].

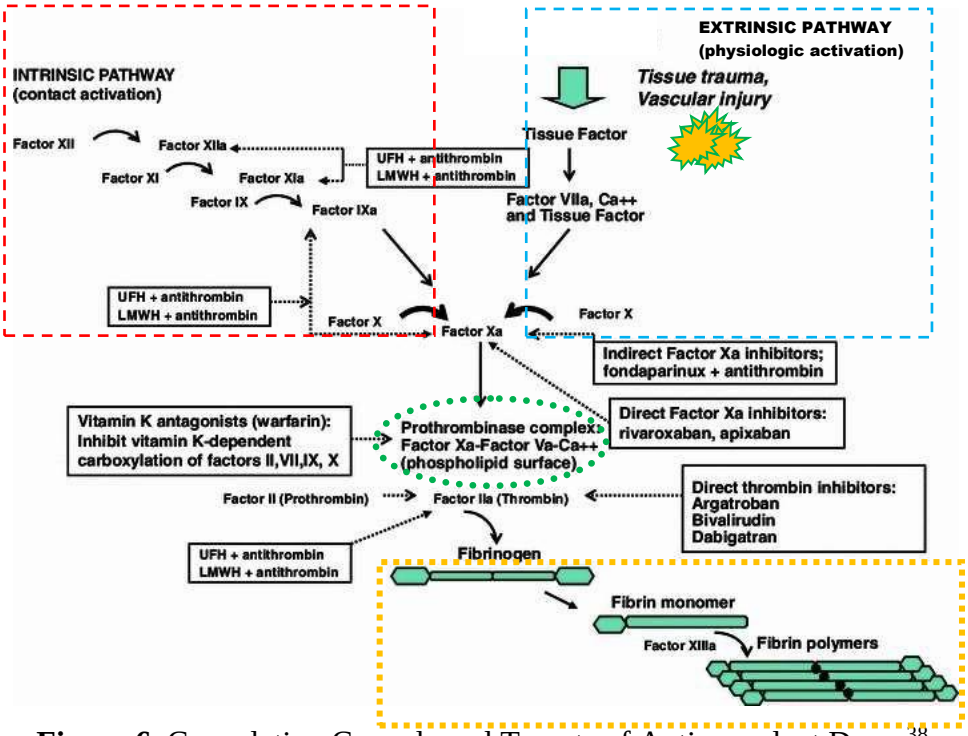

Figure 6. Coagulation Cascade and Targets of Anticoagulant Drugs[38].

Conclusion

Venous thromboembolism (VTE) is one of the most frequent complications of hospitalization and is strongly associated with morbidity, mortality and costs. Therefore, almost all ICU patients are at high risk of experiencing thrombosis. For this reason, thromboprophylaxis is necessary for these patients. The thromboprophylaxis of choice for ICU patients is LMWH. Under certain conditions, UFH or mechanical thromboprophylaxis can be considered. It is hoped that the outcome of ICU patients will improve by preventing thrombosis.

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Authors' Contributions

FR and CFRW both contributed to compiling the article, collecting journals and supporting literature, preparing the manuscript, and designing figures and

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