Prevention of Venous Thrombo-Embolism in Non-surgical Hospitalized Patients

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Abstrak

Trombo-emboli vena (TEV) umum dijumpai pada pasien rawat inap dan dipertimbangkan sebagai suatu komplikasi tidak hanya bagi pasien post bedah tetapi juga pada pasien dengan kondisi medis lainnya. Kebanyakan pasien rawat inap yang mengalami TEV ataupun emboli paru tidak menjalani prosedur bedah sebelumnya. Beberapa studi besar acak, tersamar ganda dan dengan plasebo seperti MEDENOX, PREVENT dan ARTEMIS telah memastikan manfaat dan keamanan dari tromboprofilaksis terhadap TEV terhadap pasien rawat inap dengan kondisi medis akut. Panduan tahun 2008 dari The American College of Chest Physicians (ACCP) merekomendasikan penilaian risiko bagi setiap pasien dengan kondisi medis tertentu pada saat masuk rumah sakit dan profilaksis VTE, baik dengan regimen antikoagulan ataupun pencegahan secara mekanik, sebaiknya diterapkan bagi mereka yang tergolong berisiko tinggi. Studi-studi lainnya menunjukkan bahwa banyak kasus VTE pada pasien medis terjadi setelah keluar dari perawatan rumah sakit, namun hingga kini belum ada publikasi perihal uji klinis maupun rekomendasi untuk mengevaluasi profilaksis VTE bagi pasien medis rawat jalan. Pada artikel ini, kami mencoba mengulas beberapa literatur untuk kepentingan penilaian risiko dan profilaksis VTE bagi pasien medis rawat inap. ***(Med J Indones 2010; 19:71-7)***

Abstract

Venous thromboembolism (VTE) is commonly found in hospitalized patients, considered as complication not only in surgical patients but also in medical patients. The vast majority of hospitalized patients with VTE or pulmonary embolism have not undergone any recent surgery. Several large randomized, double-blind, placebo controlled trials including MEDENOX, PREVENT and ARTEMIS have confirmed the efficacy and safety of VTE thromboprophylaxis for acutely ill medical inpatients. The American College of Chest Physicians (ACCP) Guidelines 2008 recommend a risk assessment at the time hospital admission for every medical patients and VTE prophylaxis using either anticoagulant medications or mechanical prevention should be applied for those who have high risk condition. Other studies showed that many cases of VTE in medical patients occur after hospital discharge, but still no clinical trials and current recommendation evaluating VTE prophylaxis for medical outpatients have been published yet. In this article, we attempt to review the literatures on importance of risk assessment and VTE prophylaxis for hospitalized medical patients. ***(Med J Indones 2010; 19:71-7)***

Key words: *venous thromboembolism, hospitalized patients, risk assessment, thromboprophylaxis.*

Venous Thromboembolism (VTE) constitutes a clinical spectrum encompassing Deep Vein Thrombosis (DVT) dan Pulmonary Embolism (PE). VTE accounts for more than 250,000 cases of hospitalized patients per year in the United States, with the case fatality of PE is approximately 15 %. VTE constitutes one of the most common causes of cardiovascular and cardiopulmonary illnesses, but it is often difficult to diagnose to such a degree that delays in therapy occurs. Its onset is usually unpredictable, and the likelihood of recurrence after completing a time-limited course of anticoagulation remains uncertain. Although most of the patients survive, further disability includes the potential development of chronic pulmonary hypertension or chronic venous insufficiency that will decline the patient's quality of life. [1-3]

VTE event is commonly found in hospitalized patients especially ones have undergone major orthopedic surgeries. Although VTE has traditionally been considered a surgical complication, the vast majority of hospitalized patients with symptomatic VTE have not undergone recent surgery. Actually, 70-80% of in-hospital fatal PE occurs in non-surgical patients.[4] About half the cases of VTE are idiopathic and occur without antecedent trauma, surgery, immobilization, or diagnosis of cancer.

Virchow (1858) described firstly the association between Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). PE usually comes from DVT at proximal lower extremity which can be symptomatic or asymptomatic.[2] Asymptomatic proximal leg DVT has a high associated mortality rate among patients hospitalized with medical illnesses. The 90-day mortality rate in hospitalized medical patients was 14 percent for those with asymptomatic proximal leg

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DVT at day 21, compared with a 1.9 percent 90-day mortality rate for those with no DVT at day 21. This finding underscores the appropriateness of targeting asymptomatic proximal leg DVT as an endpoint in clinical trials of thromboprophylaxis.[1]

In prospective studies of hospitalized patients at high risk who were not receiving prophylaxis, deep-vein thrombosis was found by means of venography in 10.5% to 14.9% of patients and by means of ultrasonography in 5.0% of patients. In these studies, pulmonary embolism occurred in 0.3 to 1.5% of cases, and proximal deep-vein thrombosis in 2.0 to 4.9% of cases. Thrombosis was asymptomatic in over 70% of cases, probably because most patients spent much of the day in bed, with little ambulation. Pulmonary embolism is thought to be associated with 5 to 10% of deaths of hospitalized patients, but this diagnosis is not suspected clinically in the vast majority of cases.[5]

Several gene polymorphisms are associated independently with an increased risk of VTE apart from those with widely known prothrombotic effects, such as factor V Leiden. These include polymorphisms in ADRB2, an inflammatory mediator, and LPL, an enzyme with a key role in lipid metabolism.[1] Autopsy studies have repeatedly documented the high frequency in which PE has gone unsuspected and undetected. Despite advances in diagnostic technology and therapeutic approaches, VTE remains underdiagnosed, and prophylaxis continues to be dramatically underused.[2] Therefore, risk stratification for VTE events is considerable for hospitalized patients, that is, not only for surgical patients but also for general medical patients. Prophylaxis, either pharmacologically or mechanically, is important to elude VTE caused mortality and morbidity in hospitalized patients.

VTE prophylaxis in medical inpatients

Many acutely ill medical patients, such as those with congestive heart failure, respiratory illness, and infectious or inflammatory disease, are potentially at risk of venous thromboembolism. Most patients who die from pulmonary embolism as a complication of being admitted to hospital are medical patients. Several placebo-controlled studies have investigated the efficacy of thromboprophylaxis with anticoagulant agents such as Un-Fractionated Heparin (UFH), Low Molecular Weight Heparin (LMWH) and Fondaparinux in medical patients.[6-8] The results of these trials demonstrate that UFH, Dalteparin, Enoxaparin and Fondaparinux are able to reduce the risk of VTE in medical inpatients so that the VTE prevention with these agents might be considered in the clinical setting. The aim of this article is therefore to review recent advances in thromboprophylaxis in hospitalized medical patients and discuss them in light of the recently-updated ACCP consensus guidelines.

Three large randomized, double-blind, placebo controlled trials have provided further support for the value of prophylaxis in hospitalized patients.

In Prophylaxis of VTE in Medical Patients with Enoxaparin (MEDENOX) study,[6] two doses of enoxaparin (20 mg and 40 mg s.c. o.d.) were compared with placebo in acutely ill medical patients. It was a prospective, randomized, double blind, multicenter, and placebo-controlled trial which enrolled 1,102 patients with acute medical illness. The eligible patients were above 40-year-old, recently immobilized, and had been hospitalized because of heart failure, acute respiratory failure, and also other circumstances like acute infectious disease (without septic shock), acute rheumatic disorder, or active episode of inflammatory bowel disease which were accompanied by at least one additional risk factor for VTE. The primary end point was symptomatic or asymptomatic VTE between days 1 and 14. Deep-vein thromboses (DVT) were confirmed by using contrast venography of the legs between days 6 and 14. The study showed a significant reduction in the incidence of VTE when 40 mg enoxaparin was used compared with placebo for 6–14 days (relative risk, 0.37; 95% confidence interval (CI), 0.22–0.63; $p < 0.001$), but not when 20 mg enoxaparin was used. The benefit with 40 mg enoxaparin was maintained at a 3-month follow-up (relative risk, 0.41; 95% CI, 0.25–0.68; $p < 0.001$).[6,7] No significant differences in all-cause mortality were observed between the three groups.

The Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT)[8] later confirmed the benefit of LMWH prophylaxis in hospitalized medical patients. This study enrolled patients with an acute medical condition and projected hospitalization of 4 days or longer. The population enrolled in PREVENT was a lower-risk population than that reported in MEDENOX in terms of venous thromboembolism and mortality. Eligible population was one with the age above 40 and had one of the following; acute congestive heart failure and acute respiratory failure that did not require mechanical ventilation. Patients with infection

diseases without septic shock, acute rheumatologic disorders, or inflammatory bowel disease were also included if they had one or more additional risk factor for VTE. The primary end point was symptomatic and asymptomatic VTE. In this study, compression ultrasound was used to confirm DVT. The confirmation DVT using ultrasonography is known to be less sensitive than using contrast venography, which was used in MEDINOX and ARTEMIS, but actually it is more common in clinical practice. This study showed that thromboprophylaxis with dalteparin 5000 IU daily resulted in a 45% reduction (*P*_0.0015) in the primary end point, a composite of venous thromboembolism and sudden death at day 21. Overall, thromboprophylaxis with dalteparin for 14 days resulted in the prevention of 22 events per 1000 patients treated. This benefit was observed in a broad population of medical patients and was achieved with a low risk of major bleeding.

The recent trial assessed prophylaxis with fondaparinux, a synthetic pentasaccharide with inhibitory activity specific for activated factor X. The Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS)[9] involved 849 hospitalized patients, with entry criteria similar to those in the MEDENOX trial and PREVENT. Fondaparinux (2.5 mg once daily for 6 to 14 days) almost halved the rate of venous thromboembolism (symptomatic or asymptomatic, detected by means of venography) in older ($\geq$ 60 years) acute medical patients admitted to hospital and requiring bed rest for heart, lung, or infectious or inflammatory disorders (5.6% vs. 10.5%; relative risk reduction, 47%; P = 0.03). There was also a significant reduction in the incidence of symptomatic fatal or non-fatal pulmonary embolism in the fondaparinux group compared with the placebo group (1% vs 3%, $p = 0.029$); mortality at 1 month was 6.0% and 3.3%, respectively (P = 0.06). This reduction in venous thromboembolism was achieved with a minimal risk of major bleeding complications.[5,7,9]

The results of these three randomized - double blind trials demonstrate that enoxaparin, dalteparin, and fondaparinux are all significantly superior to placebo for VTE prophylaxis in acutely ill medical inpatients. A meta-analysis of data from MEDENOX, PREVENT and ARTEMIS has been conducted by Lloyd and colleagues[10]. This meta-analysis included 5,516 patients and concluded that VTE prophylaxis with anticoagulant medication reduce the risk of any asymptomatic DVT (RR 0.51, P<0.00001) and of symptomatic proximal DVT (RR 0.45, P<0.00001) than placebo. The incidence of major bleeding in patients who received VTE prophylaxis was, however, higher than those on placebo (RR 2.00, P=0.03). There was no difference between two groups for all-cause mortality. In conclusion, use of anticoagulant VTE prophylaxis reduces the risk of both fatal and non fatal PE and DVT, and is associated with low risk of bleeding (although higher than placebo).

Several randomized studies have compared the efficacy for VTE prophylaxis of LMWH and UFH against each other in acutely ill medical inpatients. The Prevention of Thromboembolism in Medical Patients with Enoxaparin (PRIME) study[11] and the Thromboembolism Prevention in Cardiopulmonary Diseases with Enoxaparin (PRINCE) study[12] both enrolled high-risk hospitalized medical patients who were randomly received either enoxaparin 40 mg o.d. or UFH 5,000 units every 8 h. All these studies reported that 40 mg of enoxaparin (LMWH) was at least as effective as 5,000 units of UFH every 8 h for reducing the risk of VTE in patients with cardiopulmonary disease. However, some data from the studies have shown that LMWH has a better safety profile than UFH. In PRIME study[11], major bleeding events were similar between both treatment groups, but injection-site haematomas >5 cm were more frequently reported in patients who received UFH compared with those who received enoxaparin 40 mg o.d. (10.8% vs 4.6%, $p < 0.001$). Meanwhile, The ARTEMIS study[9] reported a low risk of bleeding complications when elderly acutely ill medical patients were given thromboprophylaxis with fondaparinux 2.5 mg o.d. Major bleeding occurred in one patient in the fondaparinux group (0.2%) and one in the placebo group (0.2%). Minor bleeding occurred in 11 patients (2.6%) in the fondaparinux group and four in the placebo group (1.0%).

In a meta-analysis of nine trials comparing LMWH with UFH , which included a total of 12,391 patients (8,357 of whom were enrolled in placebo controlled trials), Kanaan and colleagues reported no significant difference between LMWH-fondaparinux and UFH 5,000 units every 12 h in VTE prevention or in the incidence of major bleeding.[13] Furthermore, Wein L and colleagues found in their meta-analysis of 36 studies that UFH 5,000 units every 8 h was more effective in VTE prevention than the same dose given every 12 hours (RR 0.27, 95% CI 0.20-0.36 versus RR 0.52, 95% CI 0.28-0.96).[14] Conclusively, both UFH and LMWH are effective and safe in VTE prevention in medical inpatients. UFH 5,000 units t.i.d and LMWH

o.d. have similar clinical outcomes; both are probably superior than UFH 5,000 units b.i.d. Overall, therapy with LMWH is considered more beneficial than UFH because of once daily dosing, fewer site haematomas and lower rates of heparin-induced thrombocytopenia.

Risk Stratification and Strategy for VTE Prophylaxis

Besides accurate diagnosis and early treatment, risk assessment of VTE is essential in management of VTE for hospitalized patients. Asymptomatic deep vein thrombosis is common in both hospitalized surgical and medical patients, and sudden deaths caused by pulmonary embolism often happen as the complication before the diagnosis is suspected. Consequently, VTE risk factor assessment is recommended for every hospitalized patient, and the primary prophylaxis using highly effective regimen that lowers the risk is the best approach. The risk of VTE is related to the presence or absence of specific risk factors, and it increases if multiple risk factors are present, as in the case of most hospitalized patients. Because decisions regarding prophylaxis depend on the baseline risk, all patients should undergo a risk assessment on admission to the hospital and a reassessment when their status changes, such as after transfer to the intensive care unit or after surgery.[5]

Analyses of clinical-trial data have also contributed to clarifying which factors lead to an increased risk of VTE. A risk-factor analysis of the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) study identified a number of independent risk factors for VTE in acutely ill medical patients.[15] Cohen et al[16] grouped the risk factors into two subgroups; acute medical illness and clinical characteristic. Some acute medical illness considered as high risks for VTE are cardiac disease (myocardial infarction, heart failure), active cancer, acute respiratory disease, inflammatory bowel disease, rheumatic disease, acute infectious disease, and neurological disorders, especially stroke and spinal cord injury. Patients with spinal cord injuries have the highest incidence of VTE of any medical inpatient group, which some studies reported 60-100 % incidence of DVT in this group of patients.[16] Furthermore, other clinical conditions considered to be the risk factors for VTE are history of previous VTE, previous cancer, older age (especially > 75 years old), recent surgery or trauma, thrombophilias, venous insufficiency / varicose veins, prolonged immobility or paresis, obesity, ongoing hormone replacement therapy or oral contraception, myeloproliferative diseases, nephritic syndrome and dehydration status.

The use of risk-assessment models and implementation of evidence-based thromboprophylaxis strategies have been supported by consensus group for prevention of VTE in hospitalized patients. The American College of Chest Physicians (ACCP) guidelines,[17] published in June 2008, recommend assessment of all hospitalized medical patients for the risk of VTE and the provision of appropriate thromboprophylaxis. Furthermore, simple and clinically-relevant risk-assessment models (RAMs) are useful for clinician to facilitate VTE risk assessment (Figure 1). For every general hospital, the ACCP recommends that a formal, active strategy and written policy that addresses the prevention of venous thromboembolism (VTE) be developed (Grade 1A). The guidelines also include the use of strategies shown to increase thromboprophylaxis adherence, including the use of computer decision support systems (Grade 1A), preprinted orders (Grade 1B), and periodic audit and feedback (Grade 1C)**.** Passive methods, such as distribution of educational materials or educational meetings, are not recommended as sole strategies to increase adherence to thromboprophylaxis (Grade 1B).

For patients hospitalized with an acute medical illness such as congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, the guidelines recommend thromboprophylaxis with LMWH (Grade 1A), low-dose UFH (Grade 1A), or fondaparinux (Grade 1A). The guidelines also advise the use of mechanical VTE prophylaxis with graduated compression stockings or intermittent pneumatic compression for the patients who are contraindicated to anticoagulant thromboprophylaxis (Grade 1A).[5,17] Furthermore, the guidelines recommend against the use of aspirin alone as thromboprophylaxis against VTE for any patient group (Grade 1A). There are, however, no certain recommendations for the prophylaxis of outpatients or the use of extended anticoagulant prophylaxis for discharged medical patients.

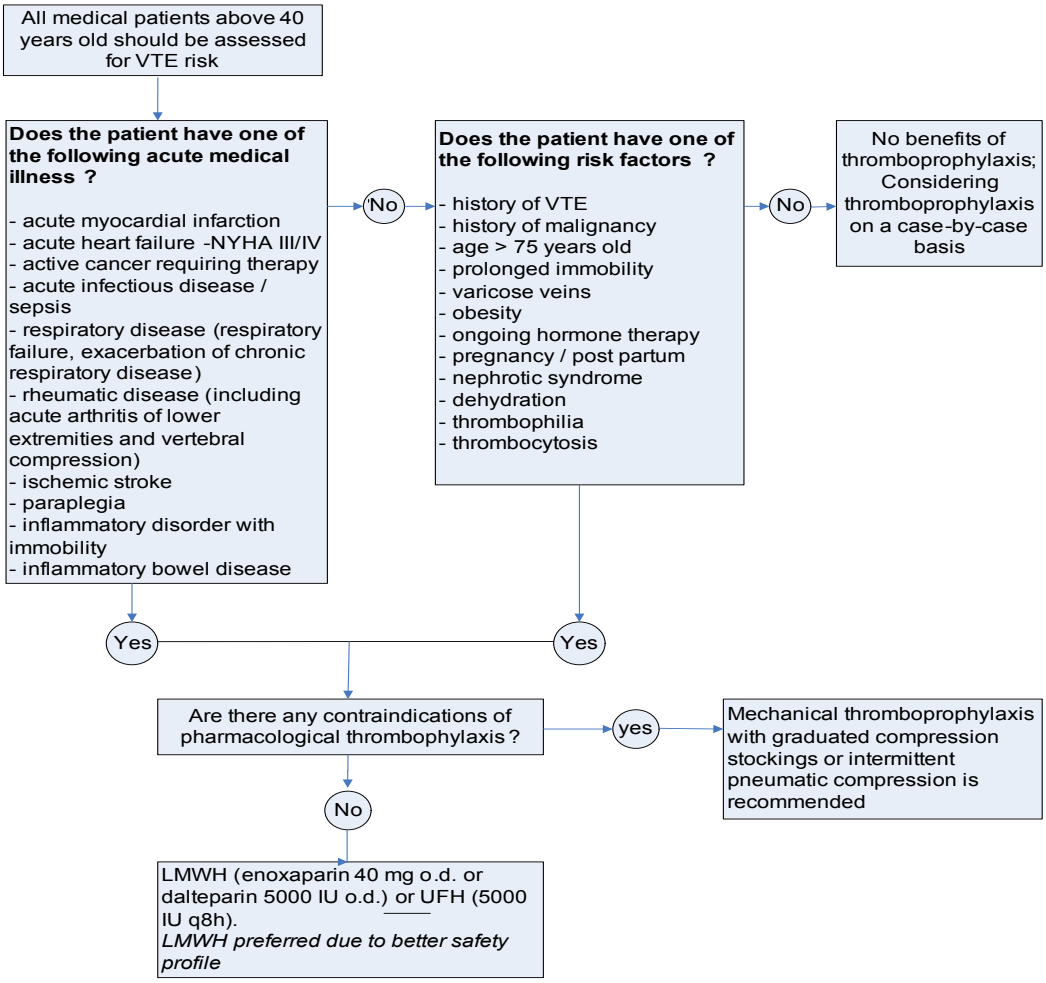

Figure 1. Risk-assessment model for VTE risk factors in non-surgical hospitalized patients

VTE Prophylaxis for Patients After Hospital Discharge

Actually, the risk of VTE does not suddenly vanish after a patient is discharged from the hospital. Data from the DVT FREE (the Prospective Registry of 5,451 Patients with Ultrasound-Confirmed Deep Vein Thrombosis) study[18] have given a new perspective of VTE. At least half of all patients who developed VTE in this study were outpatients, many of whom had been recently hospitalized. The trend in medical practice toward shorter hospital stays and the availability of outpatient therapies have made outpatient prophylaxis of acute VTE a necessity.

Spencer and colleagues later confirmed the incidence of VTE in outpatients. Their observational study published in 2007 was designed to assess the frequency of VTE in outpatients and the use of prophylaxis.[19] Of 1,897 found VTE cases, 73.7 % of cases happened in outpatients setting. Just over a third of these individuals had been hospitalized within the previous 3 months and most had been hospitalized within the past month. Only 59,7 % of outpatients who came down with VTE had received VTE prophylaxis. This study shows us that many cases of VTE occur in the outpatient setting and majority of these cases have been recently hospitalized. Hence, extended VTE prophylaxis is considered to some patients after hospital discharge.

Current ACCP guidelines (2008) recommend only extended VTE prophylaxis for particular groups of surgical patients.[17] The ACCP recommends that prophylaxis medication be extended beyond 10 days and up to 35 days after total hip replacement (grade

1A), hip fracture surgery (grade 1A) or total knee replacement (grade 2B). For patients undergoing major general surgical procedures, the guideline developers recommend that thromboprophylaxis continue until discharge from hospital (Grade 1A). For selected high-risk general surgery patients, including some of those who have undergone major cancer surgery or have previously had VTE, thromboprophylaxis after hospital discharge should be continued with LMWH for up to 28 days be considered (Grade 2A). As for patients undergoing major gynecologic procedures, the guidelines developers recommend that thromboprophylaxis continue until discharge from hospital (Grade 1A). Selected high-risk gynecology patients, including some of those who have undergone major cancer surgery or have previously had VTE, should be taken continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days be considered (Grade 2C). Extended VTE prophylaxis for medical patients, in the other hand, has not clearly recommended yet.

Since most of studies of VTE prophylaxis in medical patients applied anticoagulant medication for 6-14 days as the target prophylaxis duration and the average length of hospital stay for medical inpatients is 5-7 days, most medical inpatients will receive shorter duration of VTE prophylaxis than patients enrolled in those studies. Although the essential of VTE prophylaxis for medical patients has been well recognized, there is still lack of data or recommendations evaluating VTE prophylaxis in medical outpatients setting. This condition leads to an increase in the number of high risk outpatients, such as immobile outpatients, who are threatened by VTE. The Sirius Study[20] remarked that some personal risk factors could be considered by clinicias to extend the VTE prophylaxis medication for medical patients after hospital discharge.

CONCLUSION

Patients hospitalized with an acute medical illness such as congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease have higher risk of venous thromboembolism (VTE). Therefore, the risk assessment is essential for this group in hospital admission. VTE prophylaxis should be managed further to lower the incidence of both symptomatic and asymptomatic deep vein thrombosis in order that the sudden death in hospital caused by pulmonary embolism could be minimized. Data from several evidence based studies such as MEDENOX, PREVENT and ARTEMIS confirm the efficacy and safety of VTE prophylaxis for medical inpatients.

The American College of Chest Physicians (ACCP) guidelines 2008 recommend VTE prophylaxis for acute medical inpatients. Anticoagulant medication should be prescribed for high risk patients unless contraindications exist. The Guidelines recommend LMWH (Grade 1A), low-dose UFH (Grade 1A), or fondaparinux (Grade 1A) as anticoagulant agents for thromboprophylaxis. Several studies remarked that UFH t.i.d give the similar clinical outcomes compared with LMWH o.d. Therefore, only UFH t.i.d. and LMWH o.d. (enoxaparin or dalteparin) can be recommended for use as thromboprophylaxis in hospitalized medical patients at risk of VTE. Mechanical prevention could be used if there is any contraindication to anticoagulants.

Data from DVT FREE and Spencer et al's study show that VTE is still frequent in medical patients after hospital discharge and majority of these cases have been recently hospitalized. Therefore, extended VTE prophylaxis is considered to some patients after hospital discharge. Besides the essential of VTE prophylaxis for medical patients has been well recognized, there is still lack of data or recommendations evaluating VTE prophylaxis in medical outpatients setting. Current recommendation of extended VTE thromboembolism is just limited for some surgical patients. Further clinical trials and recommendation are needed for extended VTE prophylaxis to medical patients after hospital discharge.

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