DVT and PE Anticoagulation Prophylaxis in Medically Ill Patients

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Introduction:

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) remains a major health problem with very high mortality rate and economic toll to the U.S. health system. It is highly prevalent and is considered among the major causes for death in the U.S. Nearly one third will have a recurrent event. It is estimated that 100.000 people die each year of VTE. Almost half of VTE occurs during or after hospitalization, and PE accounts for 10% of inpatient mortality. Hospitalized medically ill patients are under significant increased risk for VTE during and after their hospital stay. Although VTE prophylaxis for medically ill inpatients is crucially important, clear guideline and standard recommendations are lacking.

This document provides up-to-date and evidence-based recommendations for the VTE prophylaxis in medically ill hospitalized patients.

Evidence:

Around 15 million patients are admitted yearly in the U.S. with a medical, non-surgical illness.[1] Close to 8 million medically ill hospitalized patients are at risk for VTE with estimated 200.000 cases reported yearly despite prophylaxis.[2,3] Factors that increase risk for VTE in medically ill hospitalized patients include age, different comorbidities, immobility, hypercoagulability and renal insufficiency. [4] Among hospitalized medically ill patients, 75% have multiple risk factors increasing VTE risk up to 8 folds than the general population.[4,5] Around 21% of these VTE cases are fatal translating into 40.000 deaths yearly.[2] 75% of fatal VTE occur in a medically ill hospitalized patients.[4] Patients admitted with VTE have longer hospital stay and higher cost (up to $50.000 in difference) than other admissions.[6] Furthermore, medically ill patients have increased VTE-related readmission rate that reaches up to 28%.[6] Based on a large retrospective analysis, more than 50% of 6 month VTE cumulative risk occurs in the first month following hospitalization, and 57% of VTE occurs post-discharge despite inpatient prophylaxis.[7]

The 2012 ACCP guidelines recommended using low molecular weight heparin (LMWH), low dose (bid or tid) unfractionated heparin (LDUH), or fondaparinux in acutely ill hospitalized patients at increased risk for thrombosis (Grade 1B).[8] Most of the trials included acutely ill hospitalized patients (mean age was >65 years), admitted for congestive heart failure (CHF), severe respiratory disease, or acute infectious, rheumatic, or inflammatory conditions who were immobilized and had at least one more risk factor (e.g. age >40, active cancer, previous VTE, or serious infection). Duration of prophylaxis use ranged from 6-21 days or discharge from hospital, whichever came first.[4] Meta-analysis of multiple trials demonstrated that anticoagulant thrombophylaxis was associated with significant reduction in fatal PE and symptomatic DVT but without significant difference for non-fatal PE, major bleeding, and all-cause mortality.[4] Based on pooled analysis data, there was no significant difference seen between LDUH and LMWH for DVT, PE, overall mortality and HIT. However, there was less bleeding events seen with LMWH.[4] There is no compelling data to suggest that LDUH tid dosing, compared with bid dosing, reduces VTE or causes more bleeding.[4] In summary, there is no clear evidence in the current literature to support choosing one form of pharmacoprophylaxis over another in the medical population based on outcomes or from a cost-effectiveness standpoint. It would be reasonable to make choices based on patient preference, compliance, and ease of administration (eg, oral vs injection, daily vs bid vs tid dosing), as well as on local factors affecting acquisition costs.[4]

VTE prophylaxis with enoxaparin (6-14 days) in medically ill patients can significantly attenuate and reduce risk of VTE from 10-20 to 2-6%. [9-

[11] VTE or VTE related mortality rate is 2 times more on day 35 compared to day 10 post-hospitalization despite receiving prophylaxis with enoxaparin. [9] Extended duration of prophylaxis with enoxaparin versus with placebo to 28 days after standard enoxaparin dosage (EXCLAIM trial) showed significant reduction of VTE but with an expense of increased major bleeding. [12] The MAGELLAN trial found that in hospitalized patients for medical illness, rivaroxaban 10 mg for 31-39 days was non-inferior at 10 days and superior at 35 days for VTE rate compared to enoxaparin 6-14 days but with more major bleeding at both 10 and 35 days.[9] The ADOPT trial showed that in medically ill patients with an additional VTE risk, apixaban 2.5 mg twice daily was not superior to enoxaparin 6-14 days for VTE or related mortality with more major bleeding.[11] In patients admitted for acute medical illness with expected moderate/severe immobility in addition to age and other risks for VTE, the APEX trial demonstrated that extended betrixaban dose for 35-42 days was superior to 6-14 days of enoxaparin for VTE or related mortality with no significant difference in major but with slightly more clinically non-major bleeding.[13] The MARINER trial showed that rivaroxaban 10 mg daily, given to medical patients for 45 days after hospital discharge, was not associated with a significantly lower risk of symptomatic VTE and related death than placebo.[14]

Mechanical methods of thrombophylaxis including graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCs), and venous foot pumps (VFPs) were mostly studied in surgical patients. Based on pooled analyses, GCS did not show significant reduction in symptomatic VTE with some increased risk for skin breakdown.[4] No good quality studies of IPV or VFP devices in hospitalized medical patients.[4] Despite the uncertain benefit, mechanical thrombophylaxis with GCC or IPCs may be preferable to no prophylaxis in patients at risk for VTE who are at high risk for bleeding.[4]

In making recommendations regarding DVT prophylaxis in hospitalized medical patients, the ACCP recommended individualized approach based on balancing the benefits of reducing VTE with the risk of bleeding using risk assessment models (RAM). ACCP 2012 guidelines used Padua Prediction Scoring system (Table 1), which includes 11 common VTE risks and categorized medical hospitalized patients as low (< 4 points) and high (≥ 4 points) risk.[15] The evidence-derived IMPROVE VTE RAM utilized seven clinical risk factors that were independently associated with VTE risk in medically ill patients. The model used 1–3 points to designate three tiers of VTE risk: low VTE risk (symptomatic VTE < 1.0 %) designated with a score of 0–1, at-risk (or moderate VTE risk) with a VTE event rate of ~1.0–1.5 % designated with a score of 2 to 3, and high VTE risk with a VTE event rate of 4% or more, designated with a score of 4 or more (Table 2)[3].

The strongest risk factors to estimate bleeding risk in medical hospitalized patients are active gastrointestinal ulcer, bleeding in 3 months before admission, and PLT count of less than $50X10^9$/L, followed by age >85 years, hepatic failure, severe renal failure, and critical care unit admission.[4] The evidence-derived IMPROVE Bleed RAM used 13 clinical and laboratory factors and designated a score of 7 or more to identify a patient cohort (~10% of the population) at high risk of bleeding (major bleed risk 4.1% vs 0.4%) (Table 3)[3]. Both validated VTE as well as bleed risk scores (Padua and IMPROVE VTE and IMPROVE Bleed RAMs) can be used during admission to determine an individual medical patient's risk of VTE and major bleeding, allowing for a tailored (patient-centric) approach to thromboprophylaxis at the bedside.[3]

Medical patients with a Padua VTE score of 4 or more or an IMPROVE VTE score of more than 2, provided that they have an IMPROVE Bleed Risk score of < 7, would be at VTE risk and would warrant pharmacologic prophylaxis during their hospital stay. Those with an IMPROVE

Bleed Risk score of 7 or more should likely receive mechanical means of prophylaxis.[3]

Based on the trial results of extended prophylaxis with either enoxaparin or DOACs, it is prudent at this time to recommend either 6-14 days of prophylaxis with LMWH, LDUH, or fondaparinux, or oral betrixaban for 35-42 days.

Recommendations:

1- For acutely ill hospitalized medical patients at increased risk of thrombosis (Padua score of ≥ 4 or IMPROVE VTE risk score of ≥3), and low risk of bleeding (IMPROVE bleeding risk score of <7), we recommend anticoagulant thromboprophylaxis with LMWH, LDUH (bid or tid), fondaparinux or betrixaban.
   a) We suggest using LMWH over LDUH.
   b) In patients with history of HIT, we suggest using fondaparinux.
   c) In patients with CrCl < 30 ml/min, we suggest using LDUH.
   d) We suggest using betrixaban as an alternative to LMWH based on medication coverage and convenience (oral vs injectable).
   e) We suggest not to use other direct oral anticoagulants.

2- For acutely ill hospitalized medical patients at low risk of thrombosis (Padua score of < 4 or IMPROVE VTE risk score of < 3), we recommend against pharmacologic or mechanical thromboprophylaxis.

3- For acutely ill hospitalized medical patients at increased risk of thrombosis (Padua score of ≥ 4 or IMPROVE VTE risk score of ≥3), who are bleeding or at risk for bleeding (IMPROVE bleeding risk score of ≥7):
   a) We recommend against anticoagulant prophylaxis.
   b) We suggest optimal use of mechanical thrombophylaxis with GCS, or IPC.
   c) When bleeding risk decreases, and VTE risk persists, we suggest that pharmacologic thrombophylaxis substituted for mechanical prophylaxis.

4- In acutely ill hospitalized patients who receive an initial course of thrombophylaxis:
   a) We suggest against extending the duration of thrombophylaxis beyond the period of patient immobilization or acute hospitalization when heparin is used
   b) We recommend extended thrombophylaxis to 35-42 days when betrixaban is used.

5- We suggest against using thrombophylaxis in chronically immobilized patients including nursing home residents.

6- For dosing, refer to table 4.

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APPENDIX

Variable	Score
Active cancer	3
Previous VTE	3
Decreased mobility	3
Thrombophilia	3
Previous trauma or surgery within that last month	2
Age≥ 70	1
Heart and/or respiratory failure	1
Ischemic stroke or acute myocardial infarction	1
Acute rheumatologic disorder and/or acute infection	1
Obesity	1
Hormonal therapy	1

Table 1: Padua predictive score for VTE among hospitalized medical patients.
Score ≥ 4: high risk for VTE
Score < 4: low risk for VTE

VTE Risk Factor	Points
Previous VT	3
Known thrombophilia**	2
Cancer***	2
Current lower limb paralysis	2
Immobilization****	1
ICU/CCU stay	1
Age >60 years	1

Table 2: IMPROVE VTE Risk Model

ICU, intensive care unit; CCU, coronary care unit. A score of 0–1 constitutes low VTE risk. A score of 2–3 constitutes moderate VTE risk. A score of 4 or more constitutes high VTE risk. ** A congenital or acquired condition leading to an excess risk of thrombosis. *** May include active cancer (excluding non-melanoma skin cancer) or a history of cancer within 5 years. **** Strict definition is complete immobilization confined to bed or chair ≥ 7 days; modified definition is complete immobilization ≥ 1 day.

Variable	Score
Active gastric or duodenal ulcer	4.5
Prior bleeding within the last 3 months	4
Thrombocytopenia (<50x10^9/L)	4
Age ≥ 85 years	3.5
Liver failure (INR>1.5)	2.5
Severe kidney failure (GFR< 30 mL/min/m^2)	2.5
Admission to ICU or CCU	2.5
Central venous catheter	2
Rheumatic disease	2
Active malignancy	2
Age: 40-84 years	1.5
Male	1
Moderate kidney failure (GFR: 30-59 mL/min/m^2)	1

Table 3: IMPROVE Bleeding Risk Score

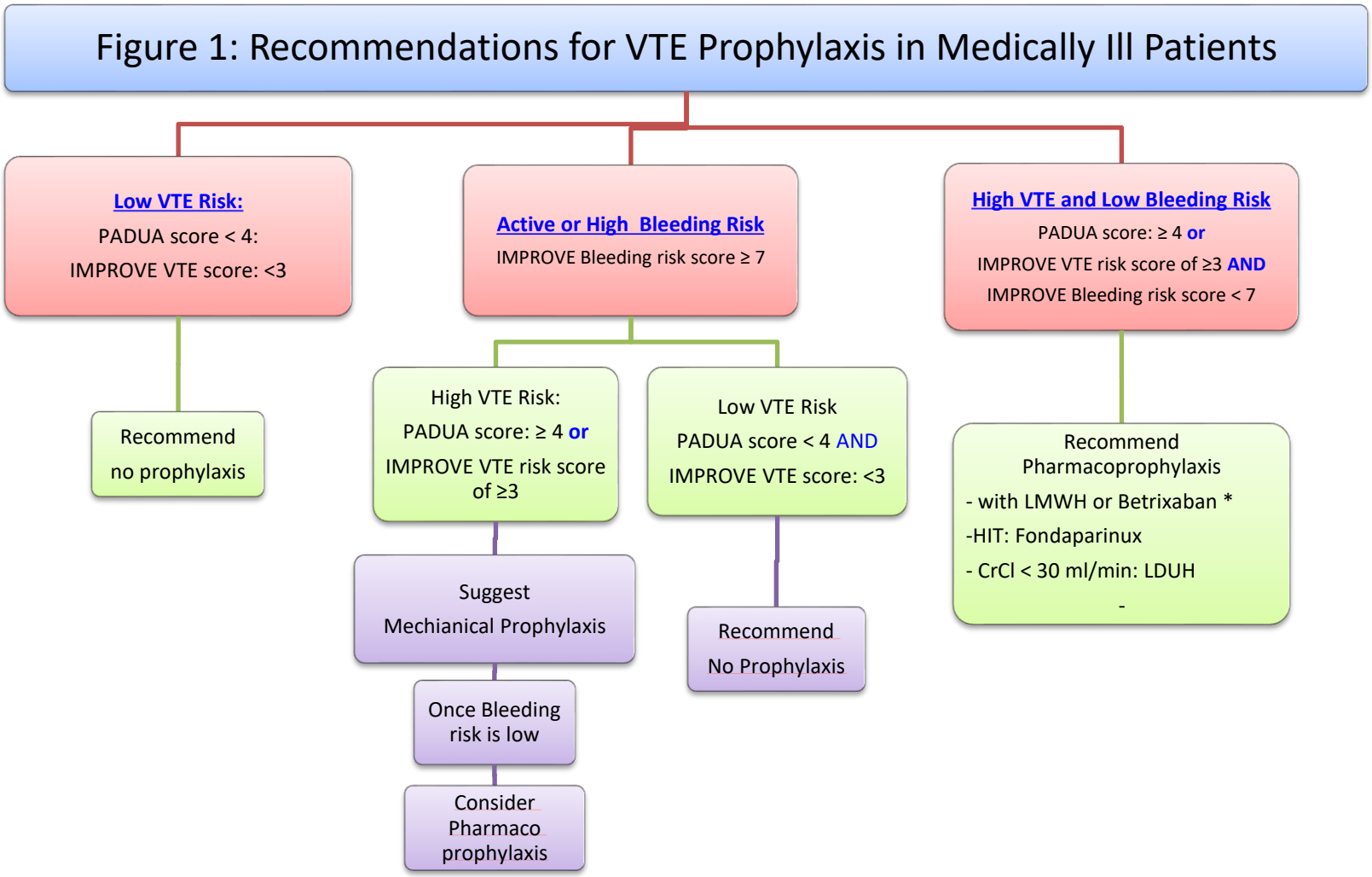
ICU, intensive care unit; CCU, critical care unit; CV, central venous; GFR, glomerular filtration rate; INR, international normalized ratio.

Interpretation: A score of 7 or more constitutes high bleed risk.

Anticoagulant	**Dose**
LDUH	<55kg or >65 years old: heparin 5000 units subcutaneous every 12 hours ≥55kg or ≥65 years old: heparin 5000 units subcutaneous every 8 hours
Enoxaparin	BMI <40 kg/m2: 40 mg SC qd BMI >40 kg/m2: 40 mg SC q12h OR 0.5mg/kg SC q12-24h
Fondaparinux	2.5 mg SC qd Should be avoided if a CrCl<30 or weight <50 kg
Betrixaban	-160 mg po first day followed by 80 mg po for 35-42 days - 80 mg po first day followed by 40 mg po for 35-42 days if concurrent use of P-gp inhibitors or CrCl of 15-30 mL/min

Table 4: Anticoagulant prophylaxis dosing information
BMI: Body mass index; CrCl: creatinine clearance; LDUH: low dose unfractionated heparin, po: oral; SC: subcutaneous.

Figure 1: Recommendations for VTE Prophylaxis in Medically Ill Patients



ESRD: End Stage Renal Disease; HIT: Heparin Induced Thrombocytopenia; LDUH: Low Dose Unfractionated Heparin, LMWH: Low Molecular Weight Heparin; VTE: Venous Thromboembolism .

***** We suggest using betrixaban as an alternative to LMWH based on medication coverage and convenience (oral vs injectable).