

Society of Hospital Medicine

Venous Thromboembolism Prophylaxis in the Hospitalized Medically Ill Patient

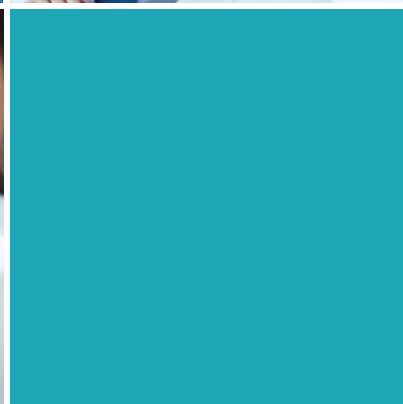
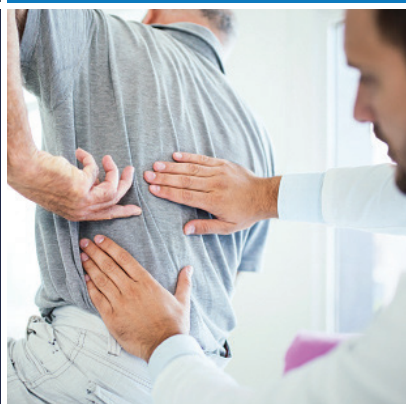


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CONTRIBUTORS

Scott Kaatz, DO, MSc, FACP, SFHM

Henry Ford Hospital

Paul Grant, MD, FACP, SFHM

Michigan Medicine

Kathryn E. Dane, Pharm.D., BCPS

The Johns Hopkins Hospital

Zachary D. Demertzis, DO

Henry Ford Hospital

BACKGROUND AND EPIDEMIOLOGY

Acute Venous Thromboembolic Disease (VTE) consisting of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) has an annual incidence in United States (US) of 1 to 2 per 1000 patient years. This rate increases with age and at 45 years old, lifetime risk is 8.1% and is higher in black, obese and sickle cell patients; 11.5%, 10.9% and 18.2% respectively. Hospital associated VTE accounts for approximately 50% of all VTE cases and the cost of preventable VTE is estimated at \$7 to \$10 billion per year in the US.¹

Major risk factors for hospital associated VTE (not an exhaustive list) in medical patients include older age, obesity, decreased mobility, infection, stroke, Congestive Heart Failure (CHF), inflammatory bowel disease and autoimmune/rheumatologic diseases and cancer. Cancer accounts for approximately 20% of cases in medical patients in and outside of the hospital. Surgical procedures account for approximately 20% of all VTE cases. VTE as a result of surgical procedures is not addressed in this compendium because we are specifically discussing hospitalized medically ill patients.¹

The 2008 Surgeon General's Call to Action to Prevent DVT and PE ushered in an era of intensified interest in VTE prophylaxis in hospitalized medical patients and was followed by The Joint Commission standards and Centers for Medicare & Medicaid Services (CMS) performance penalties.²⁻⁴ One risk with the enthusiasm for VTE prophylaxis in the hospital is the potential for overuse. While the underutilization of VTE prophylaxis is well documented, it has also been overprescribed in low-risk patients.⁵⁻⁹

In follow up to the Surgeon General's Call to Action, the American Heart Association issued a renewed Call to Action to Prevent Venous Thromboembolism in Hospitalized Patients which is summarized by the American College of Cardiology.^{1,10} There are five major goals. These goals include: a.) performance of VTE risk assessment in all hospitalized patients, b.) use of the indicator preventable VTE as a CMS benchmark for hospital comparison and pay-for-

performance programs (CMS), c.) appropriations across public and private sectors to improve public awareness of VTE, d.) national tracking of VTE with use of the standardization of definitions of VTE that occurs within 90 days of hospitalization, and e.) a central steward for VTE risk assessment, prophylaxis, and VTE rates for all hospitals.

This compendium discusses the medically ill, non-surgical hospitalized patients and reviews two changing paradigms in VTE prophylaxis: not giving prophylaxis to all patients and considering extended prophylaxis in select patients. We discuss four major topics: VTE risk stratification, in-hospital VTE prophylactic options, consideration for post-discharge prophylaxis and thromboembolic prevention in COVID-19 patients. Each section begins with a case study and a short description of what is likely the best answer followed by review of background, guidelines and select primary evidence and concludes with our bottom line. We have included appendices with deeper detail of the primary literature as well as tables that summarize these studies for those who would like to more closely review the data. This compendium may be used in conjunction with brief educational modules and supplemental resources including a checklist and order sets to support practice at your local hospital. The tools and resources will allow you to quickly access needed information that has been developed according to the best available evidence so that you can optimize the prevention of VTE for your patients.

VTE Risk Assessment

Case Study 1:

A 59-year-old male is admitted for CHF exacerbation with shortness of breath and lower extremity edema. There is no other significant past medical history. He ran out of his medications one week ago.

How would you approach VTE prophylaxis?

- A. Use a formal risk assessment model like Caprini, Padua or International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score to determine if the patient is at risk
- B. Assess VTE and bleeding risk without a formal score
- C. Give pharmacologic or mechanical prophylaxis since most hospitalized patients are at high risk
- D. Give pharmacologic or mechanical prophylaxis because CHF patients are at high risk

Short answer: Answer A is correct.

Multiple guidelines suggest or recommend assessment of VTE and bleeding risk to guide VTE prophylaxis. However, there is no one method of assessment that is agreed upon. Importantly, most hospitalized medically ill patients will be at low VTE risk when using a VTE risk assessment model/score and do NOT require prophylaxis.

Multiple societal guidelines recommend performing VTE risk assessment for all hospitalized patients. It is also stated in the American Heart Association 2020 Call to Action to Prevent VTE in Hospitalized Patients.^{1,11-13}

Based on these guidelines, if a patient has documented low risk of VTE based on a validated risk stratification tool and develops VTE, The Joint Commission does not consider this a failure.³ Despite identifying risk factors associated with VTE, prophylaxis in acutely ill hospitalized patients remains underused.^{5,8,9,14,15}

A systematic review suggests that electronic alerts are the current best option to assure VTE risk assessment is accomplished.¹⁶ All of the compendium's authors' institutions have incorporated a medical records alert system to risk-stratify medically ill patients being admitted. However, each institution uses a different risk assessment model.

Multiple VTE Risk Assessment Models (RAMs) exist, with a wide range of VTE predictions and outcomes (Supplemental Index, Table 1).¹⁷ Unfortunately, RAMs have come under question for their accuracy in their ability to risk stratify. Systematic reviews have assessed various RAMs and found variability amongst risk factors and magnitude of the individual predictors, concluding that there is lack of generalizability

and inadequate external validation of published RAMs, limiting their practical use.¹⁸⁻²⁰ The Michigan Hospital Medicine Safety Consortium collected state-wide, detailed patient-level data on VTE risk factors and outcomes, and externally validated four commonly used RAMs. These models include: Caprini, Intermountain, IMPROVE 4 factor and Padua in non-Intensive Care Unit (ICU) hospitalized medical patients. All four RAMs discriminated high-risk from low-risk patients and the 90-day clinical VTE rate was approximately threefold greater in the high-risk patients compared to the low-risk. Of interest, use of pharmacologic VTE prophylaxis did not correlate to VTE risk in this observational study.⁷

Although most RAMs have concentrated on VTE risk, simultaneously incorporating bleeding risk assessment is also important and suggested by guidelines.¹³ To our knowledge, there is no systematic review on bleeding RAMs, however, the IMPROVE bleeding RAM has been developed and two studies have externally validated it and found similar results with scores >7 showing a two-fold increase in bleeding risk (Table 1).²¹⁻²³

Table 1:
Risk Assessment Models

Caprini RAM		Kucher RAM ²⁵		Padua RAM ²⁷		IMPROVE-4 RAM ²⁸		IMPROVE-7 RAM ²⁸		IMPROVE-Bleed RAM ²¹		Geneva RAM ²⁹	
Highest Risk > 5 Moderate Risk 2 Low Risk 0-1		High Risk > 4 Low Risk 0-3		High Risk ≥ 4 Low Risk 0-3		High Risk ≥ 2 Low Risk 0-1		High Risk > 2 Low Risk 0-1		High Risk ≥ 7 Low Risk < 7		High Risk > 3 Low Risk 0-2	
RISK FACTOR	SCORE	RISK FACTOR	SCORE	RISK FACTOR	SCORE	RISK FACTOR	SCORE	RISK FACTOR	SCORE	RISK FACTOR	SCORE	RISK FACTOR	SCORE
Elective Major Lower Extremity Arthroplasty	5	History of VTE	3	History of VTE	3	History of VTE	3	History of VTE	3	Active Gastric or Duodenal Ulcer	4.5	Cardiac Failure	2
Hip/Pelvis/ Leg Fracture	5	History of Cancer	3	Active Cancer	3	Thrombophilia	3	Active Cancer	2	Recent Bleeding (<3mo)	4	Respiratory Failure	2
Stroke (<1 month)	5	Hypercoagulable State	3	Hypercoagulable State	3	Age >60yo	1	Current Lower Limb Paralysis	2	Trombocytopenia (<50 x 10 ⁹)	4	Stroke (<3 months)	2
Trauma (<1 month)	5	Major Surgery	2	Reduced Mobility	3	History of Cancer	1	Thrombophilia	2	Age >85yo	3.5	Myocardial Infarction (<4 weeks)	2
Spinal Cord Injury (<1 month)	5	Age >70yo	1	Major Surgery or Trauma (≤1 month)	2			Age >60yo	1	Hepatic Failure (INR >1.5)	2.5	Acute Infection	2
Age >75yo	3	BMI >29	1	Age >70yo	1			ICU/CCU	1	Renal Failure (GFR <30)	2.5	Acute Rheumatic Disease	2
History of VTE	3	Bed Bound	1	BMI ≥30	1			Immobilization ≥ 7 days	1	ICU/CCU	2.5	Malignancy	2
Family History of Thrombosis	3	Hormone Therapy	1	Acute Heart/ Respiratory Failure	1					Central Venous Access	2	Myeloproliferative Syndrome	2
Factor V Leiden	3			Acute Myocardial Infarction	1					Acute Rheumatic Disease	2	Nephrotic Syndrome	2
Prothrombin 20210A	3			Acute Infection/ Rheumatologic Disease	1					Current Cancer	2	History of VTE	2
Elevated Homocysteine	3			Hormone Therapy	1					Age 40-85	1.5	Hypercoagulable State	2
Lupus Anticoagulant	3									Male	1	Immobilization for 3 days	1
Elevated Cardiolipin Antibody	3									Renal Failure (GFR 30-60)	1	Recent Travel (>6 hours)	1
Heparin-Induced Thrombocytopenia	3											Age >60yo	1
Congenital/Acquired Thrombophilia	3											BMI >30	1
Age 64-75	2											Chronic Venous Insufficiency	1
Arthroscopic Surgery	2											Pregnancy	1
Cancer	2											Hormone Therapy	1
Major Surgery (>45min)	2											Dehydration	1
Laparoscopic Surgery (>45min)	2												
Immobilization (>72hrs)	2												
Plaster Cast Immobilization (>1mo)	2												
Central Venous Access	2												
Age 41-60yo	1												
Minor Surgery	1												
History of Prior Major Surgery (<1mo)	1												
Varicose Veins	1												
Inflammatory Bowel Disease	1												
Leg Swelling	1												
BMI >25	1												
Acute Myocardial Infarction	1												
Heart Failure Exacerbation (<1mo)	1												
Sepsis (<1mo)	1												
Acute Respiratory Disease (<1mo)	1												
Abnormal Pulmonary Function	1												
Active Bed Rest	1												
Ongoing Hormone Therapy	1												
Pregnant or Post-Partum (<1mo)	1												
Unexplained Stillborn or Recurrent Spontaneous Abortions	1												

RAM Accuracy

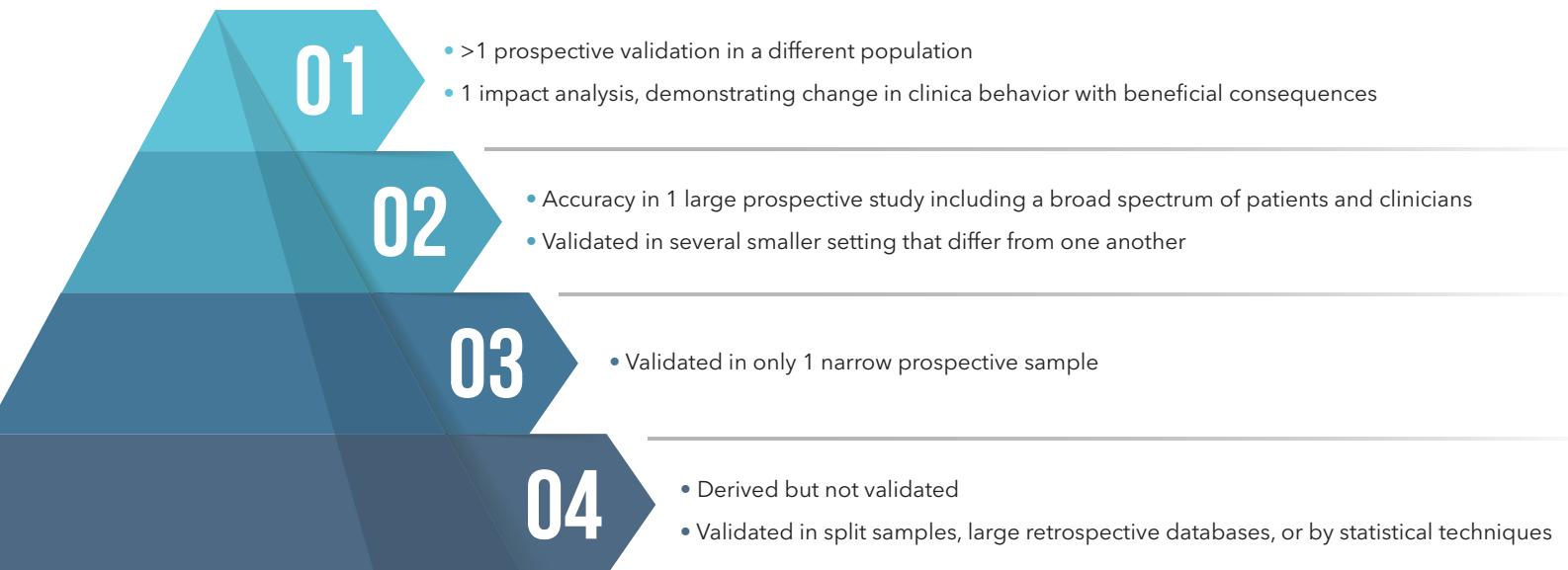
Accuracy in prognostication is fundamental to optimal patient care. Clinical experience has provided clinicians with an intuitive sense. However, intuition can often be misleading. This has led to the development and use of prediction, or RAM that simultaneously incorporate prognostic factors and estimate a patients' absolute risk of an event. In order for RAMs to achieve ideal results, they must attempt to achieve adequate discrimination, discerning high from low risk individuals from experiencing an event, and calibration, how similar the predicted absolute risk is to the observed risk in the patient population. McGinn, et al. developed a hierarchical guide for clinicians when reviewing the evidence behind RAMs (Figure 1; Hierarchy of Evidence for Clinical Decision Making). Level 1 evidence requires at least one prospective validation in a different population and one impact analysis demonstrating change in clinical behavior

with beneficial consequences, and thus can be used in a wide variety of settings. Level 2 evidence demonstrates accuracy in either one large prospective study with a broad spectrum of patients or validated in several smaller settings, leading to their use in various settings with confidence. Level 3 evidence is only narrow prospective samples, and clinicians may consider using these studies with caution if it matches their clinical setting. Lastly, level 4 evidence is derived but not validated or have undergone retrospective analysis, and these rules need further evaluation prior to application.³⁰

The key takeaway is that all hospitalized medical patients should be assessed for VTE. VTE and bleeding RAMs can assist in assessing risk, but may not definitively guide all prophylaxis decisions.

Figure 1:
Hierarchy of Evidence for Clinical Decision Making

<p>LEVEL 1: Rules that can be used in wide variety of settings with confidence that they can change clinician behavior and improve patient outcomes</p>	<p>LEVEL 2: Rules that can be used in various settings with confidence</p>	<p>LEVEL 3: Rules that can be considered using with caution and if the clinician's patients are like those in the study</p>	<p>LEVEL 4: Rules that need further evaluation before application</p>
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In Hospital VTE Prophylaxis

Patients hospitalized for acute medical illness suffer from a diverse group of disorders including infection, acute exacerbations of chronic respiratory conditions, heart failure, and rheumatologic disorders, among others. The odds of VTE occurrence increases 8-fold in hospitalized patients, and VTE in acute medically ill patients accounts for over 50% of hospital acquired events.³¹⁻³³ Furthermore, hospital mortality due to VTE exceeds 10% according to autopsy data, and as many as 80% of fatal PEs in hospitalized patients occur in acutely ill medical patients.^{34,35}

Efficacy of Pharmacologic VTE Prophylaxis Compared to Placebo

Pharmacologic prophylaxis against VTE has shown to significantly reduce rates of hospital acquired VTE compared to placebo. This has been demonstrated in small, older trials using unfractionated heparin (UFH), and more recent randomized controlled trials with a large enrollment of hospitalized medical patients comparing low molecular weight heparins (LMWHs) to placebo. The Medical patients with Enoxaparin (MEDENOX) trial was the first randomized controlled trial evaluating the safety and efficacy of VTE prophylaxis, comparing the LMWH enoxaparin with placebo in 1,102 acutely ill medical patients.³⁶ Patients were randomized to receive subcutaneous enoxaparin at 40 mg daily, 20 mg daily, or placebo for 6 to 14 days. The primary endpoint included clinical VTE and VTE found on protocol-based venographic screening at day 14 after enrollment. There was significantly less occurrence of the primary endpoint with enoxaparin 40 mg daily versus placebo (5.5% vs. 14.9%). Importantly, there was no difference in adverse events or mortality when comparing both enoxaparin dosing strategies to placebo.³⁶

Using a different LMWH, the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT) trial demonstrated VTE prophylaxis with dalteparin 5,000 units subcutaneously once daily in medically ill patients was associated with a 45% relative risk reduction in symptomatic and ultrasound screening VTE when compared to placebo.³⁷ Although dalteparin use was associated with a trend towards increased major bleeding events compared to placebo, this difference was not statistically significant.³⁷

The ARixta for ThromboEmbolism Prevention in a Medical Indications Study (ARTEMIS) trial, a randomized controlled trial evaluating the synthetic factor Xa inhibitor fondaparinux subcutaneously 2.5 mg once daily for VTE prophylaxis compared to placebo in medically ill patients, reported similar findings to both MEDENOX and PREVENT.³⁸ It should be noted all three of these trials screened for DVTs in all study patients, even those without signs or symptoms of venous thrombosis. Because routine

screening for asymptomatic VTE is not recommended in clinical practice, the event rates in these studies are likely inflated compared to symptomatic VTE event rates in real world cohorts. However, asymptomatic VTE remains a relevant clinical endpoint because development of asymptomatic VTE is associated with a significant increase in all-cause mortality compared to patients without asymptomatic proximal DVT.³⁹

Available data from meta-analyses corroborate the findings of these three landmark randomized controlled trials evaluating pharmacologic VTE prophylaxis compared to control, demonstrating a 48-57% relative risk reduction in PE, including a 56% relative risk reduction in fatal PE, and a 48-56% relative risk reduction in DVT.⁴⁰⁻⁴² A meta-analysis conducted by Lloyd et al. demonstrated VTE prophylaxis was associated with a 2-fold increase in major bleeding compared to placebo. Although this finding was not consistently reproduced in other similar publications, it should not be discounted, as this meta-analysis included several randomized controlled trials including three of the landmark trials previously mentioned (MEDENOX, PREVENT, and ARTEMIS). Unlike the postsurgical patient population, VTE prophylaxis has not demonstrated a reduction in VTE-related mortality in medically ill patients to date, likely due to the increased number of comorbidities contributing to acute illness in hospitalized medical patients.⁴³

Despite the proven benefits of pharmacologic VTE prophylaxis over placebo, VTE prophylaxis is underutilized in many eligible acutely ill medical patients. Reported rates of appropriate VTE prophylaxis prescribing in hospitalized patients at risk for VTE range from 16-60%.^{5,8,9} Factors associated with increased use of appropriate VTE prophylaxis for medically ill patients include immobilization, the presence of at least one VTE risk factor, and increased length of stay, among others.⁸ Appropriate VTE prophylaxis prescribing rates are lower in medically ill patients when compared to surgical patients, potentially owing to the increased number of comorbidities and the complexity of VTE risk assessment in this patient population.⁵ This underscores the importance of standardizing institutional guidelines and protocols to increase identification of patients at risk for VTE as well as optimizing prophylaxis agent selection and dosing.

Low Molecular Weight Heparin vs. UFH in Acute Medically Ill Patients

Case Study 2:

A 62-year-old male weighing 80 kg with active rheumatoid arthritis is admitted to the ward for treatment of pneumonia. He is moderately ill and has reduced mobility secondary to weakness and arthritis. He is not receiving concomitant antiplatelet or anticoagulation therapy and has normal liver and kidney function. He is considered high risk for VTE and low risk for bleeding.

What would you use for VTE prophylaxis for this patient on the ward?

- A. UFH 5,000 units subcutaneously twice daily
- B. UFH 5,000 units subcutaneously three times daily
- C. Enoxaparin 40 mg subcutaneously once daily
- D. Enoxaparin 40 mg subcutaneously once daily plus pneumatic sequential compression devices

Short answer: Answer C is correct.

Meta-analyses have shown lower rates of VTE and major bleeding with LMWH compared to heparin in acute medically ill patients. Therefore, guidelines suggest using LMWH over heparin and not combining with mechanical prophylaxis such as pneumatic sequential compression devices.

The most frequently prescribed agent for VTE prophylaxis varies between institutions, and head-to-head data comparing the safety and efficacy of UFH vs. LMWH are conflicting (Table 2).^{8,9} These inconsistent results are likely secondary to the heterogeneity of pharmacologic VTE prophylaxis agents and dosing strategies utilized within treatment groups. Perhaps the most compelling of these studies is the Cochrane review performed by Alikhan et al. in 2014.⁴⁴ This analysis demonstrated when compared to UFH, enoxaparin is associated with a 33% reduction in the odds of VTE (95% CI 0.62-0.96, P=0.02) and a 57% reduction in major bleeding events (95% CI 0.22-0.83, P=0.01). Additional data suggest LMWH use is also associated with fewer injection site hematomas compared to UFH.⁴⁵

Although not demonstrated in medical patients specifically, indirect evidence in surgical patients suggests LMWH is also associated with a 76% reduction in the risk of HIT compared to UFH.⁴⁶ Additionally, traditional LMWH dosing for VTE prophylaxis requires once daily administration, offering more efficient drug administration and less patient discomfort over UFH administration two to three times per day. Missed doses of prescribed VTE prophylaxis in acutely ill hospitalized patients is not uncommon due to patient refusal and other factors. LMWH products are associated with significantly lower rates of missed doses compared to UFH, likely owing to patient preference for fewer daily injections.⁴⁷ These findings, as well as current national guidelines, support preferential use of LMWH over UFH for VTE prophylaxis in acutely ill hospitalized patients without a contraindication to anticoagulation.^{13,48}

Low Molecular Weight Heparin vs. UFH in Critically Ill Patients

Case Study 3:

The patient above (62-year-old male weighing 80 kg with active rheumatoid arthritis and associated limited mobility who is receiving treatment for pneumonia), is transferred to the intensive care unit due to worsening respiratory status and acute renal failure requiring initiation of renal replacement therapy. He is still considered high risk for VTE and low bleeding risk.

What would you use for VTE prophylaxis for this patient in the intensive care unit?

- A. UFH 5,000 units subcutaneously twice daily
- B. UFH 5,000 units subcutaneously three times daily
- C. Enoxaparin 40 mg subcutaneously once daily
- D. Enoxaparin 40 mg subcutaneously once daily plus pneumatic sequential compression devices

Short answer: Answer B is correct.

As with acute medically ill patients on the wards, LMWH has also demonstrated superior efficacy to UFH in critically ill patients. However, this patient has acute renal failure and because UFH undergoes significantly less renal elimination than LMWH, UFH would be preferred in this scenario due to limited data for LMWH use in patients with severe renal impairment and in the setting of renal replacement therapy. Data suggest UFH 5,000 units TID is more effective than 5,000 units BID and is preferred for this reason.

Critically ill patients are at particularly high risk for VTE. A randomized controlled trial conducted in critically ill adults with sepsis demonstrated symptomatic lower extremity DVT and PE occur in 5.8% and 0.8% of patients within 28 days follow-up, respectively, when not receiving pharmacologic VTE prophylaxis.⁴⁹ The high event rate in the critically ill population is likely secondary to an accumulation of VTE risk factors, including infection, acute inflammatory response, the presence of central venous access devices, severe immobility, and occasionally paralysis in select patients. The Prophylaxis of Thromboembolism in Critical Care (PROTECT) trial was a landmark trial evaluating the use of dalteparin 5,000 units subcutaneously once daily compared to UFH 5,000 units subcutaneously twice daily in critically ill

patients, the majority of whom were medical patients. In this trial, dalteparin use was associated with a significant reduction in pulmonary emboli compared to UFH, and no difference in rates of proximal DVT, major bleeding, or mortality between the two groups.⁵⁰ These findings have been corroborated in multiple meta-analyses demonstrating LMWH prophylaxis use in critically ill patients is associated with a reduction in VTE events with no difference in major bleeding rates observed between the two agents.⁵¹ As with acute medically ill patients, LMWH is preferred over UFH in critically ill patients for these reasons. However, despite the benefit of LMWH prophylaxis over UFH, many critically ill patients experience acute kidney injury, and UFH is preferred over LMWH in this scenario as described in the below special populations section.

Low Molecular Weight Heparin Dosing

The optimal LMWH dosing strategy for VTE prophylaxis in acutely ill medical patients is 40 mg subcutaneously once daily. The efficacy of this regimen was demonstrated in the MEDENOX trial, which randomized patients to receive LMWH 40 mg subcutaneously once daily, LMWH 20 mg subcutaneously once daily, or placebo.³⁶ While LMWH 40 mg daily resulted in significantly lower VTE rates compared to placebo, this reduction was not maintained when comparing LMWH 20 mg daily to placebo. The preferred dalteparin dosing strategy is 5,000 units subcutaneously once daily.^{37,50}

UFH Dosing

The preferred UFH dosing strategy (5,000 units three times per day versus 5,000 units twice per day) has historically been subject to greater debate. Although the pharmacokinetic profile of UFH (half-life of 1-2 hours) would support three times per day dosing over twice per day dosing, data evaluating the efficacy of these two dosing strategies are conflicting. Two studies demonstrated a significant reduction in VTE with administration UFH 5,000 units twice per day compared to placebo.^{52,53} However, two additional studies failed to demonstrate the efficacy of UFH 5,000 units twice per day over placebo, and one randomized controlled trial found UFH 5,000 units twice per day to have equivalent efficacy to enoxaparin 20 mg daily (a dosing strategy shown to be less efficacious than enoxaparin 40 mg daily).⁵⁴⁻⁵⁶ Conversely, both studies evaluating UFH 5,000 three times per day versus placebo have demonstrated a significant reduction in VTE with the intervention.^{57,58}



A meta-analysis of 36 studies concluded UFH 5,000 units three times per day demonstrated superior efficacy compared to UFH 5,000 units twice per day, with a 63% reduction in DVT associated with use of the former; however, this improved efficacy was accompanied by an increased risk of bleeding.⁴⁵ A second meta-analysis of twelve studies showed a trend towards reduced rates of PE with UFH 5,000 units three times per day vs. twice per day but this result was not statistically significant.⁵⁹ The American College of Chest Physicians (2012), American Society of Hematology (2018) guidelines for VTE prophylaxis in acutely ill medical patients, and International Union of Angiology guidelines (2013) do not state a preference for three times per day or twice per day UFH dosing.^{13,48,60} Taken together, the available data suggests UFH 5,000 units three times per day should be considered over UFH 5,000 units twice per day except for in patients deemed high risk of bleeding where less aggressive dosing may be considered to reduce bleeding risk.

Low Molecular Weight and UFH Use in Special Populations

Data evaluating UFH and LMWH dosing in underweight or obese acute medically ill patients are extremely limited. Although treatment doses of both UFH and LMWH are weight-based, fixed dosing is used for VTE prophylaxis, which could contribute to underexposure or overexposure in obese or underweight patients, respectively. Despite this, current guidelines do not provide dosing recommendations for pharmacologic thromboprophylaxis in extremes of weight.^{13,48}

Obesity

Case Study 4:

A 55-year-old female is admitted to the intensive care unit for septic shock. She weighs 140 kg and has a body mass index of 48 kg/m².

What would you use for VTE prophylaxis?

- A. UFH 5,000 units subcutaneously three times daily
- B. Enoxaparin 40 mg subcutaneously twice daily
- C. Enoxaparin 60 mg twice daily
- D. Fondaparinux 5 mg subcutaneously once daily

Short answer: Answer B is correct.

Although data evaluating optimal VTE prophylaxis dosing in obese patients are overall limited, especially in acutely ill medical patients, enoxaparin data from the bariatric surgery population suggest 40 mg subcutaneously twice daily dosing is reasonable in patients with BMI 40-49 kg/m². For patients with BMI > 50 kg/m², enoxaparin 60 mg subcutaneously twice daily should be considered. Given the paucity of data in the acute medically ill patient population, it is reasonable to extrapolate from the bariatric surgery dosing in the acute medically ill population. An alternative enoxaparin regimen of 0.5 mg/kg subcutaneously q12h has been studied in several retrospective analyses of surgical patients, and is recommended by some experts in obese patients. Based on limited data, UFH 7,500 units q8h or dalteparin 7,500 units subcutaneously once daily may be considered. Fondaparinux data in obesity are limited and therefore fondaparinux should be avoided in this setting if possible.

Most studies evaluating enoxaparin dosing in obesity were conducted in the bariatric surgery population and are retrospective analyses. The majority of these studies used anti-Xa levels as a surrogate measure of efficacy, which is a limitation because the target anti-Xa level for prophylaxis dosing is poorly defined and target anti-Xa level achievement for VTE prophylaxis has not been associated with improved clinical outcomes. Based on these data, enoxaparin 40 mg twice daily should be considered in patients with BMI 40-49 kg/m², and enoxaparin 60 mg twice daily may be considered in patients with BMI 50 kg/m² or higher.^{61,62} Alternatively, some experts suggest weight-based enoxaparin 0.5 mg/kg twice daily dosing in obese patients based on retrospective data from other populations.⁶³⁻⁶⁵ Although not well correlated with clinical events, steady state peak anti-Xa monitoring and dose adjustment to target a peak anti-Xa level of

0.2-0.5 IU/mL may be used in obese patients deemed high risk for bleeding or thrombosis. Even less data is available to guide UFH and dalteparin dosing in obesity, and the target anti-Xa range for thromboprophylaxis is not well established for this agent. A retrospective study in morbidly obese patients undergoing bariatric surgery (BMI > 40 kg/m² or > 35 kg/m² with at least one significant co-morbidity) suggests dalteparin 7,500 units subcutaneously once daily results in anti-Xa levels within the desired range for the majority of patients.⁶⁶ Similarly, increased UFH dosing to 7,500 units three times per day should be considered in patients with BMI > 40 kg/m² based on the results of one retrospective study.⁶² Fondaparinux should be avoided in obesity due to the paucity of data evaluating the efficacy of standard or increased intensity dosing in this population.

Low Body Weight

Case Study 5: A 34-year-old female is admitted for a cystic fibrosis exacerbation. She weighs 38 kg.

What would you use for VTE prophylaxis?

- A. UFH 5,000 units subcutaneously two times daily
- B. UFH 5,000 units subcutaneously three times daily
- C. Enoxaparin 30 mg subcutaneously once daily
- D. Enoxaparin 40 mg subcutaneously once daily

Short answer: Answer C is correct.

Available retrospective data suggest that standard doses of enoxaparin and UFH are associated with increased bleeding events and/or supratherapeutic anti-Xa levels in underweight patients. One small retrospective study suggests enoxaparin 30 mg daily dosing is likely to achieve appropriate drug concentrations in patients weighing < 55 kg.

Data evaluating pharmacologic thromboprophylaxis dosing in underweight patients are sparse, but enoxaparin has been evaluated more in this setting than other available agents. When evaluating enoxaparin dose-response, an inverse relationship between anti-Xa levels and body weight has been reported. In one study, enoxaparin 40 mg daily dosing resulted in supratherapeutic anti-Xa levels in 61% of patients weighing 55 kg or less, and 85% of patients weighing 45 kg or less.⁶⁷ While this suggests enoxaparin dose reduction is prudent in underweight patients, data defining the most appropriate dose adjustment are lacking. However, in one small retrospective study of patients < 55 kg, 74% of patients achieved anti-Xa levels within goal with a median dose of enoxaparin 30 mg subcutaneously once daily.⁶⁸ With these findings considered, it is reasonable to utilize enoxaparin 30 mg daily dosing in patients weighing 55 kg or less, and as with obese patients, steady state peak anti-Xa monitoring may be considered.⁶¹

Extremely limited data exist evaluating reduced UFH dosing in underweight patients, but standard UFH 5,000 units two- or three-times daily dosing has been associated with increased bleeding risk in two small retrospective studies.^{69,70} Based on this, it is reasonable to utilize reduced UFH doses of 2,500 units twice (up to three times) daily in this population. Therapeutic drug monitoring with steady state anti-Xa peak levels may be considered to further inform UFH dose adjustments in underweight patients. Lastly, fondaparinux and dalteparin have not been evaluated in underweight patients and should therefore be avoided in favor of enoxaparin or UFH if possible.



Renal Impairment

Renal function must be considered when selecting pharmacologic thromboprophylaxis. Both enoxaparin and dalteparin have increased reliance on renal elimination compared to UFH. Very limited high-quality data exist evaluating LMWHs in patients with renal dysfunction, especially in patients with creatinine clearance < 20 mL/min or requiring hemodialysis, and patients with creatinine clearance < 30 mL/min were generally excluded from landmark clinical trials evaluating LMWH.⁷¹ A subgroup analysis of the PROTECT trial, which compared VTE prophylaxis with dalteparin versus UFH in critically ill patients, compared the efficacy and safety of both agents in patients with severe renal dysfunction.⁷² There was no difference in rates of major bleeding between groups in patients with creatinine clearance < 30 mL/min or when further narrowing the population to include patients with end stage renal disease. Additionally, rates of any VTE were not different between groups for patients with creatinine clearance < 30 mL/min or end stage renal disease, but patients with creatinine clearance < 30 mL/min receiving dalteparin experienced higher rates of DVT. However, these findings are from a *post hoc* analysis of a randomized controlled trial and therefore should be applied with caution.

Notably, although all LMWHs do undergo renal elimination, the degree of reliance on renal elimination differs among agents according to molecular weight, and therefore the findings from the PROTECT subgroup analysis evaluating dalteparin cannot be extrapolated to other LMWHs.⁷¹ If enoxaparin is utilized in patients with renal impairment, dose reduction to 30 mg once daily is required for patients with a creatinine clearance < 30 mL/min. No dose adjustment recommendations exist for dalteparin in renal impairment, although the use of dalteparin for extended durations in patients with renal impairment has not been evaluated and therefore the risk of accumulation over time with repeated dosing cannot be excluded. Use of the synthetic pentasaccharide, fondaparinux, is contraindicated in patients with creatinine clearance < 30 mL/min because 75% of fondaparinux elimination occurs via the renal route. Because of disadvantages of alternative prophylaxis agents in patients with renal impairment and limited data for the use of LMWHs in this population, UFH remains the preferred agent in this setting.



Heparin-Induced Thrombocytopenia

Heparin-Induced Thrombocytopenia (HIT) is a life-threatening adverse reaction to heparin products and should be considered when patients receiving heparin experience a 50% drop in platelet count from baseline occurring 5 to 10 days after the first day of heparin exposure.⁷³ HIT occurs more commonly in surgical patients than medical patients, and therefore the majority of data describing HIT risk factors come from the surgical population. LMWH is associated with a 76% reduction in HIT incidence when compared to UFH in post-surgical patients.⁴⁶ Though data in medically ill patients are more limited, 75% of the PROTECT trial population was comprised of medically ill patients, and dalteparin use reduced HIT incidence by 73% compared to UFH.⁵⁰ When there is a high

clinical suspicion for HIT according to clinical scoring tool, all sources of heparin should be discontinued (including VTE prophylaxis), and therapeutic intensity anticoagulation should be initiated with a heparin-alternative while awaiting the results of HIT laboratory testing. Data describing the risk of HIT recurrence with heparin product re-exposure in remote HIT are limited, and therefore current guidelines recommend avoidance of heparin products for VTE prophylaxis in this population.⁷³ Fondaparinux is a synthetic pentasaccharide not associated with the development of HIT and is therefore the preferred agent for VTE prophylaxis in patients with remote HIT. Based on the ARTEMIS trial results, the optimal dose of fondaparinux for prophylaxis is 2.5 mg subcutaneously



Mechanical Prophylaxis

Non-pharmacologic (or mechanical) options for VTE prophylaxis include graduated compression stockings and intermittent pneumatic compression devices. The efficacy and safety data supporting mechanical VTE prophylaxis options is limited and has primarily been studied in the surgical patient population. In acutely ill medical patients, the largest body of evidence evaluating mechanical prophylaxis is in patients with acute stroke. Current guidelines recommend mechanical prophylaxis be considered only for patients at risk of VTE and with a contraindication to pharmacologic prophylaxis. However, these guidelines state no preference between the use of graded compression stockings and intermittent pneumatic compression devices for mechanical prophylaxis.^{13,48} Although no strict absolute contraindications exist for pharmacologic VTE prophylaxis (with the exception of significant active bleeding), the following are potential indications to withhold prophylactic anticoagulation based on expert opinion:

- Use of systemic therapeutic anticoagulation
- Hemophilia or presence of other significant bleeding disorders
- Platelet count < 50K
- INR > 2.0
- Active intracranial lesions/neoplasm
- Intracranial hemorrhage within the past 3-6 months
- Gastrointestinal or genitourinary hemorrhage within the last month

The addition of mechanical prophylaxis to pharmacologic thromboprophylaxis is not recommended, as this approach has been studied and has not proven to be beneficial.^{74,75} Mechanical prophylaxis with thigh-length graduated compression stockings was compared to a control group receiving no graduated compression stockings in a randomized controlled trial of patients with immobility following acute stroke Clots in Legs Or sTockings after Stroke (CLOTS 1). In this study, the use of thigh-length graduated compression stockings was shown to increase the odds of development of skin breakdown, ulcers, blisters, or skin necrosis 4-fold, and was not effective in preventing symptomatic or asymptomatic proximal VTE compared to control.⁷⁶ The use of thigh-length versus below-knee compression stockings for VTE prophylaxis were compared in hospitalized patients with acute stroke in the CLOTS 2 trial.⁷⁷ Thigh-length stockings significantly reduced rates of proximal symptomatic or asymptomatic VTE compared to below-knee stockings, but skin breakdown was numerically higher in patients receiving thigh-length stockings. The CLOTS 3 randomized controlled trial evaluated the safety and efficacy of intermittent pneumatic compression devices compared to control in immobile patients hospitalized with acute stroke and found intermittent pneumatic compression devices were effective in reducing rates of symptomatic or asymptomatic proximal VTE at the cost of increased rates of skin breakdown.⁷⁸ Additionally, there is a paucity of data comparing the safety and efficacy of graded compression stockings to intermittent pneumatic compression stockings in medically ill patients. Based on the findings of the three CLOTS trials, the use of mechanical prophylaxis should be carefully considered because this intervention is not without risks including skin breakdown. Mechanical prophylaxis is also associated with increased cost, patient discomfort leading to poor compliance, and reduced ambulation.⁷⁹ Despite the narrow patient population qualifying for mechanical VTE prophylaxis according to national guideline recommendations, and the associated risks of this intervention, mechanical VTE prophylaxis is over-utilized. If mechanical VTE prophylaxis is indicated due to high bleeding risk in patients also considered high risk for VTE, intermittent pneumatic compression devices or thigh-high graded compression stockings should be considered. Additionally, there is no role for the addition of mechanical prophylaxis to pharmacologic prophylaxis in hospitalized medically ill patients.”

Meta-Analyses Comparing Safety and Efficacy of LMWH vs. UFH for VTE Prophylaxis in Hospitalized Medically Ill Patients Risk Assessment

STUDY	DESIGN	INTERVENTIONS	OUTCOMES	COMMENTS
Mismetti 2000 ⁴¹	Meta-analysis of nine RCTs (n=4,669)	LMWH vs. UFH	DVT: 2.04% vs. 2.42% (RR 0.83; 95% CI, 0.56-1.24, p=0.37) Clinical PE: 0.34% vs. 0.60% (RR 0.74; 95% CI, 0.29-1.88, p=0.52) Clinical PE: 0.34% vs. 0.60% (RR 0.74; 95% CI, 0.29-1.88, p=0.52)	UFH dosing strategy varied from 10,000-15,000 units/day. LMWH agent and dosing differed between studies.
Kanaan 2007 ⁸⁰	Meta-analysis of four RCTs (n=4,034)	Enoxaparin vs. UFH	DVT: OR 0.92; 95% CI, 0.56-1.52 PE: OR 0.8; 95% CI, 0.22-2.9 VTE: OR 0.89; 95% CI, 0.54-1.46 VTE-related death: OR 0.76, 95% CI, 0.36-1.6 Major bleeding: OR 0.69; 95% CI, 0.29-1.68	UFH dosing strategy was 10,000 units/day in all four studies. Enoxaparin dosing included 20 mg/day, 40 mg/day, and 36 mg TID.
Wein 2007 ⁴⁵	Meta-analysis of ten RCTs (n=5,299)	LMWH vs. UFH	DVT: RR 0.68; 95% CI, 0.52-0.88 PE: RR 0.57; 95% CI, 0.25-1.34 Mortality: RR 1.16; 95% CI, 0.85-1.59 All bleeding: RR 0.83; 95% CI, 0.6-1.14 Injection site hematoma: RR 0.47; 95% CI, 0.36-0.62	UFH dosing strategy varied from 10,000-15,000 units/day. LMWH agent and dosing differed between studies.
Bump 2009 ⁸¹	Meta-analysis of five RCTs (n=3,921)	LMWH vs. UFH	DVT: RR 0.90; 95% CI, 0.57-1.43 PE: RR 0.82; 95% CI, 0.26-2.63 Mortality: RR 0.96; 95% CI, 0.50-1.85 All bleeding: RR 0.72; 95% CI, 0.44-1.16	UFH dosing strategy varied from 10,000-15,000 units/day. LMWH agent and dosing differed between studies.
Laporte 2011 ⁸²	Meta-analysis of four RCTs (n=3,600)	Enoxaparin 40 mg/day vs. UFH	Total VTE: RR 0.63; 95% CI, 0.51-0.77 Symptomatic VTE: RR 0.38; 95% CI, 0.17-0.85 Symptomatic PE: RR 0.37; 95% CI, 0.13-1.02 Major bleeding: RR 1.13; 95% CI, 0.53-2.44 All-cause mortality: RR 0.83; 95% CI, 0.64-1.08	UFH dosing strategy varied from 10,000-15,000 units/day.
Lederle 2011 ⁸³	Meta-analysis of nine RCTs (n=11,650)	LMWH vs. UFH	Symptomatic DVT: 0.16% vs. 0.16% (RR 0.1.00; 95% CI, 0.20-4.94) PE: 0.52% vs. 0.74% (RR 0.70; 95% CI, 0.44-1.11) Major bleeding: 2.1% vs. 2.3% (RR 0.89; 95% CI, 0.70-1.15) Mortality: RR 9.3% vs. 10.2% (RR 0.91; 95% CI, 0.73-1.13)	UFH dosing strategy varied from 10,000-15,000 units/day. LMWH agent and dosing differed between studies.
Alikhan 2014 ⁴⁴	Meta-analysis of six RCTs (n=5,942)	LMWH vs. UFH	DVT: OR 0.77; 95% CI, 0.62-0.96 Non-fatal PE: OR 0.93; 95% CI, 0.42-2.08 Fatal PE: OR 0.33; 95% CI, 0.01-8.14 Major bleeding: OR 0.43; 95% CI, 0.22-0.83 All-cause mortality: OR 0.79; 95% CI, 0.54-1.16	UFH dosing strategy varied from 10,000-22,500 units/day. LMWH agent and dosing differed between studies.

RCT: randomized controlled trial
LMWH: low molecular weight heparin
OR: odds ratio

UFH: unfractionated heparin
DVT: deep vein thrombosis
PE: pulmonary embolism

VTE: venous thromboembolism
CI: confidence interval
RR: relative risk

Post Discharge Prophylaxis

Case Study 6:

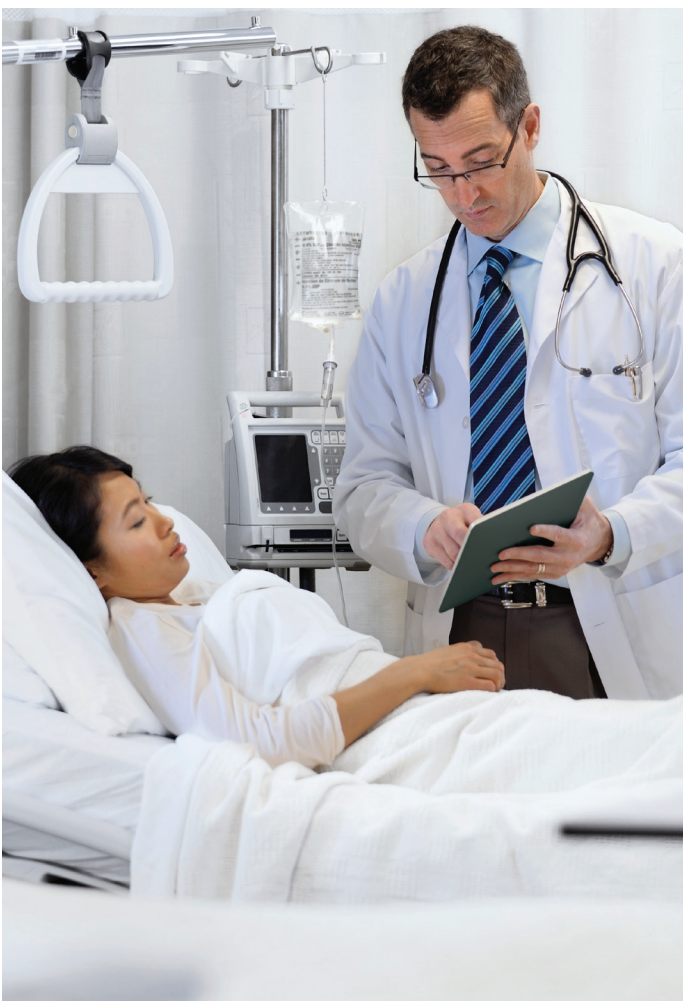
A 72-year-old admitted for CHF is ready for discharge on hospital day 7. The patient will require home physical therapy for generalized weakness and has a history of osteoarthritis of hips. The patient had provoked PE two years ago after knee replacement surgery and completed three months of anticoagulation at that time. The patient has normal kidney and liver function. The patient received enoxaparin prophylaxis as an inpatient.

What would you do for VTE prophylaxis at discharge?

- A. Enoxaparin 40 mg qd for 2 weeks
- B. Apixaban 2.5 mg bid for about 1 month
- C. Rivaroxaban 10 mg qd for 31-39 days
- D. No need for post discharge prophylaxis

Short answer: Answer C or D is correct.

Guidelines recommend not using extended prophylaxis. The only FDA approved and available anticoagulant for extended prophylaxis is rivaroxaban at the dose and duration above.



VTE prophylaxis has become the standard of care for at-risk hospitalized patients with landmark trials supporting a thromboprophylaxis duration ranging from 6 to 14 days.³⁶⁻³⁸ Although extending prophylaxis to the post-discharge setting has not been common practice, it has been well established that the risk for VTE events continues for greater than 1 month after hospital discharge.⁸⁴ For over a decade, researchers have studied post-discharge VTE prophylaxis in patients hospitalized with acute medical illness. Finding the appropriate patient population to effectively balance VTE risk reduction without excessive bleeding has been challenging, but significant progress has been made. In fact, two oral anticoagulants (betrixaban and rivaroxaban) have received FDA-approval for extended VTE prophylaxis in acutely ill medical patients post hospital discharge. Of note, betrixaban is no longer manufactured or available.

Key Clinical Trials

The first major trial to study the efficacy and safety of extended VTE prophylaxis for acutely ill hospitalized medical patients was the Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization (EXCLAIM) trial.⁸⁵ This was an international randomized controlled trial (RCT) of almost 6,000 patients with risk factors for VTE who received enoxaparin 40 mg daily for an initial 10 +/- 4 days, followed by an additional 28 +/- 4 days of either enoxaparin 40 mg daily or placebo. Although extended use of enoxaparin decreased VTE events, bleeding rates were significantly higher. Although a potential net benefit was observed in some patient subgroups (e.g. patients with significant immobility, age greater than 75 years, and women), enoxaparin use for post-hospital discharge prophylaxis has not been adopted or approved.

With the development of direct oral anticoagulants (DOACs), the concept of post-discharge VTE prophylaxis was further explored as a more practical option than injectable agents such as enoxaparin. The factor Xa-inhibitor apixaban was the first DOAC to be studied in a large RCT (n=6,528) for this indication in the Apixiban Dosing to Optimize Protection from Thrombosis (ADOPT) trial.⁸⁶ Hospitalized patients with risk factors for VTE were randomized to apixaban 2.5 mg twice daily for 30 days versus enoxaparin 40 mg once daily for 6 to 14 days. While there was no difference in VTE events, patients receiving apixaban experienced significantly more major bleeding.

Similar to the ADOPT trial, The Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin (MAGELLAN) trial studied the factor Xa-inhibitor rivaroxaban against enoxaparin in 8,101 hospitalized medical patients at risk for VTE.⁸⁷ While extended use of rivaroxaban (35 +/- 4 days) was more effective than a shorter course of enoxaparin (10 +/- 4 days) for VTE prevention (the relative risk reduction was 23%), it was associated with a significantly higher risk of bleeding.

Rivaroxaban was again studied in The Medically Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolism Risk (MARINER) trial, a RCT of over 12,000 hospitalized medical patients at increased risk for VTE as determined by a modified IMPROVE score +/- d-dimer values.⁸⁸ This trial, which was the last of the five trials, incorporated lessons from previous experience and included 3 key differences; a) patients were randomized at time of discharge allowing more precise risk assessment, b) only clinical VTE was assessed (no screening for asymptomatic DVT was performed) and c) based on a sub-group analysis of MAGELLAN, 5 key bleeding risk conditions were identified and used as exclusion criteria to improve safety. These 5 risk factors included: active cancer, dual antiplatelet therapy, severe bronchiectasis or pulmonary cavitation, an active gastroduodenal ulcer, or bleeding within 3 months. Upon hospital discharge, patients were randomized to receive either rivaroxaban 10 mg once daily (with dose adjustment for renal insufficiency) or placebo for 45 days. While there was no difference in the primary efficacy outcome (a composite of symptomatic VTE or death due to VTE), there was significantly less symptomatic nonfatal VTE events, a prespecified secondary outcome. Importantly, the incidence of major bleeding was low in patients randomized to rivaroxaban (0.28%) and not significantly different than placebo.

In the above trials that studied the efficacy and safety of extended VTE prophylaxis, higher bleeding rates were routinely observed with exposure to DOACs. In a recent subgroup analysis of the MAGELLAN trial, the authors re-evaluated the risk-benefit profile after excluding patients with 5 risk factors for major bleeding noted above.⁸⁹ By excluding these patients (which accounted for approximately 20% of the total study population), major bleeding was significantly reduced while the efficacy of rivaroxaban was maintained (non-inferior to enoxaparin at 10 days, and superior at 35 days in reducing VTE and VTE-related death).

In large part due to this secondary analysis of the MAGELLAN trial, the FDA approved rivaroxaban in October 2019 for VTE prophylaxis in acutely ill patients. The FDA labelling for rivaroxaban includes initiation during hospitalization and continuing post-discharge. The approval was for patients at elevated risk for VTE but not deemed to be at high risk of bleeding.

Another oral factor Xa-inhibitor, betrixaban, was studied in the Acute Medically Ill VTE (Venous Thromboembolism) Prevention with Extended Duration Betrixaban (APEX) trial.⁹⁰ This was a RCT of over 7,500 patients hospitalized for acute medical illness who were randomly assigned to either enoxaparin 40 mg once daily for 10 +/- 4 days or betrixaban 80 mg once daily for 35 to 42 days which was started during hospitalization. In the analysis, patients were risk stratified using age and d-dimer levels. While this trial did not reach statistical significance with respect to the primary efficacy outcome of VTE reduction in the pre-specified primary patient cohort (patients with an elevated d-dimer level), a benefit was seen in the trial's two larger patient cohorts (a 20% relative risk reduction in patients with an elevated d-dimer level or an age of ≥ 75 years, and a 24% relative risk reduction in all enrolled patients). Importantly, there was no difference in major bleeding between betrixaban and enoxaparin.

The results of the APEX trial led to the FDA approval of betrixaban for VTE prophylaxis in adult patients hospitalized for an acute medical illness with risk factors for VTE. Although betrixaban received FDA approval in 2017, production has since been discontinued and it remains unclear if it will become available again in the future.

A recent meta-analysis was conducted to further understand the efficacy and safety of DOACs versus LMWH for VTE prophylaxis in hospitalized medical patients.⁹¹ This analysis included 3 trials; ADOPT, MAGELLAN, and APEX. The results demonstrated that while DOACs appeared to reduce the risk of asymptomatic DVT, they did not reduce the risk of PE or symptomatic DVT when compared to LMWH. The authors concluded that the use of DOACs in hospitalized medical patients slightly increases the risk of major bleeding with no appreciable benefit over LMWHs. This meta-analysis informed the American Society of Hematology (ASH) 2018 guidelines that recommend against the use of DOACs during hospitalization, and against extending pharmacological prophylaxis after hospital discharge.¹³ However, this guideline also states that further research is needed to evaluate DOACs for short-term (inpatient) and extended use for VTE prophylaxis.

A dedicated bleeding risk assessment is advised in order to safely prescribe rivaroxaban for post discharge prophylaxis. The bleeding risk elements studied in the subgroup analysis of the MAGELLAN trial by Spyropoulos et al. should be included in this assessment (e.g. active cancer, dual antiplatelet therapy, severe bronchiectasis or pulmonary cavitation, an active gastroduodenal ulcer, or bleeding within 3 months).⁸⁹

Once the patient is deemed to be at lower risk of bleeding, but is also at an elevated risk for VTE, rivaroxaban at 10 mg once daily is a suitable, FDA-approved option for VTE prevention both in the hospital and for post-hospital discharge, to complete a total combined course of 31-39 days.

COVID-19 Thromboembolic Prophylaxis

Case Study 7:

A 62-year-old with moderate COVID-19 is admitted to the floor needing 4 L nasal cannula oxygen. There is no other significant medical history. The patient has normal liver and kidney function and no increased bleeding risk. The patient's weight is 80 Kg.

What would you use for VTE prophylaxis?

- A. Do VTE risk assessment to determine if prophylaxis is indicated
- B. Prophylactic dose LMWH such as enoxaparin 40 mg qd
- C. Intermediate dose LMWH such as enoxaparin 40 mg bid
- D. Intermediate dose heparin such as 7500 units tid
- E. Therapeutic dose LMWH such as enoxaparin 80 mg bid

Short answer: Answer E is correct.

The three multiplatform trials showed an increase in oxygen support free days (decrease in the need for high flow oxygen, invasive or non-invasive mechanical ventilation, vasopressor support, extracorporeal membrane oxygenation [ECMO] or death) with therapeutic anticoagulation compared to usual care with prophylactic or intermediate dose LMWH or heparin.

In an autopsy study early in the pandemic, alveolar capillary microthrombi were seen nine times more than patients who died from influenza. This concept of micro-thrombi reduction in addition to VTE prevention can explain the primary outcomes of many anticoagulant trials in COVID-19. The use of higher than prophylactic anticoagulant doses in hospitalized patients with COVID-19 targets not only the macro vessels (DVT, PE, MI, and stroke) but also micro vessel thrombosis.

Many patients at the beginning of the pandemic would receive prophylactic or intermediate dose LMWH/heparin on the floor with dose escalation for ICU patients. D-dimer was commonly used to guide the intensity of pharmacologic VTE prophylaxis given the high rates of VTE being reported.

With the high rates of thromboembolic disease in COVID-19, intuitively, sicker patients or those with elevated biomarkers like d-dimer would seem to

require higher doses of anticoagulant prophylaxis. Trials comparing therapeutic dose LMWH or heparin (for renal failure patients) to usual care were stratified by d-dimer level with the thought that low d-dimer patients may not need therapeutic dosing. Critically ill patients were randomized to therapeutic dose LMWH/heparin or usual care in patients needing the above ICU level of care with the thought these patients might receive more benefit than moderately ill patients. ICU patients were also randomized in another trial to intermediate vs. prophylactic dose LMWH/heparin to test this dosing strategy. Finally, a trial in ICU and non-ICU patients tested therapeutic doses of a DOAC compared to prophylactic LMWH/heparin.

The above practice and hypotheses about prophylaxis for COVID patients proved to be wrong in late summer 2021 (at the time of this writing), with the full publication of the trials (outlined in greater detail below), emphasizing why robust clinical trials are required to guide practice.

Therapeutic LMWH or Heparin in Moderately Ill COVID-19

The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19 (ACTIV-4a) and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) trial investigators harmonized their protocols and outcomes.⁹² These three platform trials investigate moderately ill patients that did not need ICU level support of high flow oxygen, mechanical ventilation with or without intubation or vasopressor support. Patients were further stratified based on d-dimer levels. 2,219 patients from nine countries (approximately half from US) were randomized from April 2020 to January 2021 to therapeutic LMWH (94.8%)/heparin or standard of care (71.7% low dose prophylaxis, 26.5% intermediate dose). The absolute improvement in survival until discharge without the need for ICU level organ support was 4.0%. For d-dimer sub-groups (d-dimer > 2 times local normal, < 2 times and unknown); the probability of improvement was 97.3%, 92.9% and 97.3% for high, low and unknown respectively. Major bleeding with therapeutic dosing was 1.9% vs. 0.9%.

Bottom line: Therapeutic anticoagulation primarily with LMWH improved survival to hospital discharge without the need for ICU level of care escalation by 4% (number needed to treat = 25).

Therapeutic Rivaroxaban in Moderately Ill COVID-19

The Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION) trial randomized 615 patients at 31 centers in Brazil from June 2020 to February 2021 that were hospitalized with COVID-19.⁹³ Stable patients (94%) received rivaroxaban 20 mg daily (adjusted for renal dysfunction or azithromycin) for 30 days or prophylactic dose LMWH/heparin which was extended at the treating clinicians discretion. Unstable patients (6%) started with therapeutic or LMWH/heparin and transitioned to rivaroxaban when stable in patients randomized to the intervention arm. The primary efficacy outcome was a hierarchical analysis of time to death, duration of hospitalization or duration of supplemental oxygen; the primary safety outcome was major or clinically relevant non-major bleeding through 30 days. There was no difference in efficacy and there was more bleeding with therapeutic anticoagulation (8% vs. 2%, P=0.001).

Bottom line: Therapeutic rivaroxaban did not improve the time to death, time in the hospital or duration of oxygen therapy and caused more bleeding. This trial was done mostly in moderately ill patients.



Therapeutic Dose Heparin/LMWH in Critically Ill COVID-19

In the three platform trials discussed above, 1098 (analyzed) patients from 10 countries (approximately 15% from US) with critically ill COVID-19 were randomized from April 2020 to December 2020 to open label therapeutic or usual care pharmacologic thromboprophylaxis.⁹⁴ LMWHs were the molecule of choice in approximately 90% of both strata and usual care dosing was per local practice with 40% using standard prophylactic dosing and the remainder with intermediate or higher doses, for 14 days or until hospital discharge or discontinuation of oxygen. The primary outcome was the number of days a patient was free from organ support with high flow nasal oxygen > 20 L/min, non-invasive or invasive mechanical ventilation, ECMO or vasopressor/inotrope support or death at 21 days.

The median number of organ support free days where a higher number is better, was 1 in the therapeutic anticoagulation and 4 in the usual care group. The trial was stopped early based on pre-specified interim analysis which showed 99.9% probability of futility, meaning it was very unlikely that continuing the trial would show benefit for therapeutic dose. There was no difference in hospital survival (62.7% and 64.5%; probability of inferiority 89.2%) in the therapeutic anticoagulation and usual care respectively. Major bleeding based on International Society on Thrombosis and Haemostasis was a secondary endpoint and occurred in 3.8% and 2.3% with an 87.2% probability of harm.

Bottom line: Therapeutic dose LMWH or heparin for primary prophylaxis to decrease the need for organ support with high flow oxygen, invasive or non-invasive ventilation, ECMO, vasopressor/inotrope support or death was not better than usual care and had a trend toward worse outcome and should not be used in patients with severe COVID-19.

Intermediate Dose LMWH in ICU Patients

The Intermediate vs Standard-Dose Prophylactic Anticoagulation in Critically-ill Patients With COVID-19: An Open Label Randomized Controlled Trial (INSPIRATION) trial randomized 600 (562 included in the analysis) patients in 10 Iranian ICUs to intermediate dose enoxaparin (1 mg/kg daily) or standard prophylactic dose (enoxaparin 40 mg/kg daily) with modification for body weight and creatinine clearance.⁹⁵ Primary thromboembolic composite outcome was VTE, arterial thrombosis, ECMO or mortality, bleeding outcome was major bleeding (Bleeding Academic Research Consortium type 3 or 5) and thrombocytopenia with platelet count < 20,000 at 30 days. Primary efficacy occurred in 45.7% and 44.1% of patients in the intermediate and standard dose groups (P=.70) respectively. Major bleeding rates were higher with intermediate dosing 2.5% and 1.4% which did not meet the prespecified non-inferiority margin. More patients receiving intermediate dosing had severe thrombocytopenia (2.25 vs. 0%, P=0.1).

Bottom line: Intermediate dose enoxaparin at 1 mg/kg per day did not improve thromboembolic events, tended to cause more bleeding and there was more severe thrombocytopenia in critically ill COVID-19 patients.

CONCLUDING REMARKS

VTE continues to be one of the most common causes of preventable mortality for the hospitalized medical patient. Prevention of VTE is a vital component of inpatient care and requires a comprehensive understanding of the most recent and evolving literature. The information included in this compendium provides evidence-based and practical information for the practicing hospitalist.

Key points:

- Accurate VTE risk stratification is critical. Several validated VTE risk assessment models are available and must be used to ensure patients are receiving appropriate anticoagulation. This will avoid both overuse and underuse of anticoagulation which are both common problems for the hospitalized medical patient.
- While low-molecular-weight heparin is the preferred agent for VTE prophylaxis for most hospitalized patients, it is important to be familiar with special patient populations where alternate dosing or agents are indicated. This includes patients with obesity, low body weight, renal impairment, and heparin-induced thrombocytopenia
- Post-discharge VTE prophylaxis should be considered for patients at persistently elevated risk for VTE while at an acceptable bleeding risk. Rivaroxaban is an FDA-approved anticoagulant with a VTE prophylaxis dosing option for this indication.
- COVID-19 infection has demonstrated to increase the risk of VTE. While the data is evolving, anticoagulation treatment with either full or prophylactic dosing may be indicated but depends on the patient's severity of illness (i.e., critically ill vs moderately ill patients with COVID-19 infection).

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| Appendices

Supplemental Index for Table 1

(Details of RAMs)

CAPRINI

Caprini et al., initially composed a RAM based on an observational study of 538 surgically admitted patients which he then further modified years later. Weighted risk factors included: 5 points for elective major lower extremity arthroplasty, hip/leg/pelvic fracture within 1 month, stroke within 1 month, trauma within 1 month, and acute spinal cord injury; 3 points for age greater than 75 years old, previous VTE, family history of VTE, Factor V Leiden, Prothrombin 2021A, elevated homocysteine, lupus anticoagulant, elevated cardiolipin antibodies, heparin-induced thrombocytopenia, and congenital or acquired thrombophilia; 2 points for age between 61 and 75 years old, arthroscopic surgery, cancer, major surgery duration greater than 45 minutes, laparoscopic surgery greater than 45 minutes, immobilization greater than 72 hours, immobilizing cast for greater than 1 month; 1 point for age between 41 and 60 years old, minor surgery, major surgery within 1 month, varicose veins, inflammatory bowel disease, leg swelling, body mass index >25, acute myocardial infarction, acute congestive heart failure, acute sepsis, acute lung disease, history of abnormal pulmonary function test, current bed rest, ongoing hormonal therapy, pregnancy or 1-month post-partum, and history of unexplained stillborn or recurrent spontaneous abortions. Those with a score greater than 5 were considered highest risk for VTE development, 3-4 were high risk, 2 moderate risk, and 0-1 were low risk.^{1,2}

The Michigan Hospital Medicine Safety Consortium externally verified the Caprini RAM in a retrospective study of 63,548 patients assessing its utility in predicting VTE in hospitalized medical patients³. The overall rate of VTE among patients receiving pharmacologic prophylaxis (1.03%) was not significantly different from those who did not receive treatment (1.09%; $p=0.45$). What they found was a linear relation between risk of VTE and Caprini scores from 0 to 10. Although they were unable to determine

a Caprini score threshold for VTE prophylaxis, a borderline decrease in odds of VTE with pharmacologic prophylaxis was noted for the entire population (OR, 0.85; 95% CI, 0.72- 0.99; $p=0.04$).³

KUCHER

Kucher et al. conducted a randomized control trial reviewing 2,361 patients at increased risk for VTE (score >4) based on weighted scores for assigned risk factors: 3 points for cancer, prior VTE, or hypercoagulability; 2 points for major surgery; and 1 point for age >70 years old, body mass index >29, bed bound, or hormone replacement/oral contraception. These risk factors were pulled from the electronic medical record in an automated fashion to calculate risk and send an alert regarding their high-risk status. Patients randomized to have an alert generated showed higher likelihood of receiving prophylaxis (33.5% vs 14.5%, $p<0.001$). VTE occurred in 4.9% of the alert group compared to 8.2% in the non-alert group, VTE at 90 days by 41% (HR 0.59, 95% CI 0.43-0.81, $p=0.001$).⁴

PADUA

Barbar et al. classified 1,180 hospitalized patients as high (score ≥ 4) or low (score < 4) risk for VTE based on their devised RAM (modified from the Kucher model) known as the Padua Prediction Score. Three points were assigned for: active cancer, previous deep VTE, reduced mobility (bedrest with bathroom privileges for 3 days), or known thrombophilia disease; 2 points for recent (≤ 1 month) trauma and/or surgery; and 1 point for age 70 years or older, acute heart and/or respiratory failure, acute myocardial infarction and/or stroke, acute infection and/or rheumatologic disorder, body mass index > 30, and ongoing hormonal therapy. After their risk assignment, patients were then screened for their appropriate prophylaxis and monitored for 90 days for VTE. Of the patients who were classified high-risk, 2.2% developed VTE while on appropriate prophylaxis (95% CI, 0.8-5.4) compared to 11.8% developing VTE in the

inadequate prophylaxis group (95% CI, 7.8-15.1). High risk individuals receiving appropriate VTE prophylaxis had an 80% risk reduction (crude RR 0.2, 95%, 0.07-0.52) of VTE events, and a hazard ratio of 0.13 (95% CI, 0.04-0.4, $p < 0.001$). When comparing the high to low-risk inadequate prophylaxis groups, the crude relative risk of VTE development was 38.9 (95% CI, 10.4-146.5). Barbar et al also compared their RAM to Kucher's, 243 patients deemed high-risk in the Padua RAM would've been considered low-risk in Kucher's, 9 of which developed VTE (3.7%, 95% CI, 1.7-6.9). The Padua Prediction Score showed that those without VTE prophylaxis had greater than 30-fold risk of developing VTE complications, with twice as many patients being classified high-risk compared to Kucher's RAM.⁵

IMPROVE

The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) was designed to examine VTE prophylaxis practices and clinical outcomes in patients hospitalized for an acute medical illness with a range of diagnoses.⁶ Two separate RAMs were created – one at time of admission and one during hospitalization – to predict 3-month VTE risk. They conducted a multiple regression analysis of 15,156 patients across 12 counties and 52 hospitals, determining the incidence of VTE within a 3-month following hospitalization and set their threshold of high VTE rate to align with the American College of Chest Physicians (ACCP) recommendations.⁷ Patients with ACCP-defined risk for whom VTE prophylaxis was indicated had a median risk score of 2, thus the IMPROVE RAMs suggest scores ≥ 2 during hospitalization may benefit from thromboprophylaxis.

4-Factor IMPROVE at time of admission

In the predictive model, factors most strongly related to VTE risk by 3 months post-hospitalization at the time of admission included age >60 years old (HR 1.8, CI 95% 1.2-2.7, χ^2 8.5, $p = 0.004$), cancer (HR 2.0, CI 95% 1.3-3.1, χ^2 11.0, $p = 0.001$), previous VTE (HR 5.0, CI 95% 3.3-7.8, χ^2 53.0, $p < 0.001$), and thrombophilia (HR 5.2, CI 95% 1.3-21.5, χ^2 5.2, $p = 0.02$). Age >60 -years-old and cancer were assigned 1 point, while previous VTE and thrombophilia receive 3 points each.

7-Factor IMPROVE during hospitalization

The associative model incorporates independent factors present prior and during hospitalization that are strongly linked to a 3-month VTE rate. Factors included were age >60 -years-old (HR 1.7, 1.1-2.6, χ^2 6.3, $p = 0.01$), intensive care or cardiac care unit (HR 1.8, CI 95% 1.1-2.9, χ^2 6.1, $p = 0.01$), immobilization for > 7 days (HR 1.9, CI 95% 1.3-2.7, χ^2 11.0, $p = 0.001$), current cancer (HR 2.8, CI 95% 1.9-4.2, χ^2 27, $p < 0.001$), current lower-limb paralysis (HR 3.0, CI 95% 1.6-5.7, χ^2 11.0, $p = 0.001$), known thrombophilia (HR 3.5, CI 95% 1.1-11.0, χ^2 5.2, $p = 0.04$), and previous VTE (HR 4.7, CI 95% 3.0-7.2, χ^2 48.0, $p < 0.001$). The 7-Factor IMPROVE RAM assigned 3 points for previous VTE; 2 points for current cancer, current lower-limb paralysis, and known thrombophilia; 1 point for age >60 -years-old, intensive care or cardiac care unit, and ≥ 7 -day immobilization.

IMPROVE Bleed

A multi-national observational sub-analysis of the IMPROVE study conducted by Decousus et al., assessed the rate of in-hospital major and nonmajor, but clinically significant, bleeding events, resulting in the formation of a Bleed Risk RAM.⁸ Characteristics at admission that were independent factors associated with increased bleed risk were active gastroduodenal ulcer (OR 4.15, 95% CI, 2.21-7.77), recent bleeding (within 3 months)(OR 3.64, 95% CI, 2.21-5.99), thrombocytopenia (OR 3.37, 95% CI, 1.84-6.18), age greater than or equal to 85 years old (OR 2.96, 95% CI, 1.43-6.15), hepatic failure (OR 2.18, 95% CI, 1.10-4.33), renal failure GFR <30 (OR 2.14, 95% CI, 1.44-3.20), ICU/CCU admission (OR 2.10, 95% CI, 1.42-3.10), central venous catheter (OR 1.85, 95% CI, 1.18-2.90), rheumatic disease (OR 1.78, 95% CI, 1.09-2.89), current cancer (OR 1.78, 95% CI, 1.20-2.63), age between 40 and 85 years old (OR 1.72, 95% CI, 0.91-3.25), male sex (OR 1.48, 95% CI, 1.10-1.99), and renal failure GFR of 30-60 (OR 1.37, 95% CI, 0.97-1.92). Observed bleeding rate by risk score began to escalate exponentially with scores greater than 7, thus defining the cut off score for high-risk individuals. High bleeding risk was observed in 9.7% of the patients and they had a major bleeding rate within 14 days of 4.1% compared to 0.4% in low bleeding (score <7) patients.

GENEVA

The Geneva RAM was designed by incorporating previous proposals and the Seventh Consensus Conference of the ACCP.⁹⁻¹² They found 19 factors associated with increased VTE risk: 2 points for cardiac failure, respiratory failure, recent stroke (within 3 months), recent myocardial infarction (within 4 weeks), acute infectious disease, acute rheumatic disease, malignancy, myeloproliferative syndrome, nephrotic syndrome, history of VTE, and known hypercoagulable state; 1 point for immobilization (<30-minute/day walking) for ≥ 3 days, recent travel (>6 hours), age >60-years-old, body mass index >30, chronic venous insufficiency, pregnancy, hormonal therapy, and dehydration. A retrospective validation study found that a cut-off score of 3 points or more necessitated VTE prophylaxis (agreement coefficient kappa 0.88).¹³

The Geneva RAM underwent a 1,478 patient, multicenter prospective validation study compared to the Padua Prediction RAM by Nendaz et al.¹⁴ 65% of

patients were considered high risk with the Geneva, while 48% were classified as such with the Padua score. Of those classified as high-risk, 62% received VTE in the Geneva RAM group and 61% with Padua. Occurrence of VTE within 90 days of discharge occurred in 3.2% (CI 95%, 2.2-4.6%) in the high-risk Geneva group, while 0.6% (CI 95%, 0.2-1.9%) in the low-risk Geneva group ($p=0.002$). In the Padua RAM, 3.5% developed VTE (CI 95%, 2.3-5.3%) in the high-risk while 1.1% (CI 95%, 0.6-2.3%) in the low-risk ($P=0.002$). High-risk VTE patients based on the Geneva score were univariately associated with VTE development within 90 days (HR 5.3, CI 95%, 1.61-17.48, $p=0.006$) and predicted occurrence through use of thromboprophylaxis (HR 5.52, CI 95%, 1.66-18.3, $p=0.005$). The Padua score similarly showed univariately associated with VTE development (HR 3.28, CI 95%, 1.46-7.38, $p=0.004$) and predicted occurrence with thromboprophylaxis (HR 3.33, CI 95%, 1.48-7.5, $p=0.004$). The Geneva RAM similarly risk stratified patients for VTE development in comparison to the Padua RAM¹⁴.

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Table 2:
RAM Table Condensed

Caprini RAM		Padua RAM		IMPROVE-4 RAM		IMPROVE-7 RAM		IMPROVE-Bleed RAM	
Highest Risk > 5 Moderate Risk 2		High Risk 3-4 Low Risk 0-1		High Risk ≥ 2 Low Risk 0-1		High Risk > 2 Low Risk 0-1		High Risk ≥ 7 Low Risk <7	
RISK FACTOR	SCORE	RISK FACTOR	SCORE	RISK FACTOR	SCORE	RISK FACTOR	SCORE	RISK FACTOR	SCORE
Elective Major Lower Extremity Arthroplasty	5	History of VTE	3	History of VTE	3	History of VTE	3	Active Gastric or Duodenal Ulcer	4.5
Hip/Pelvis/ Leg Fracture	5	Active Cancer	3	Thrombophilia	3	Active Cancer	2	Recent Bleeding (<3mo)	4
Stroke (<1 month)	5	Hypercoagulable State	3	Age >60yo	1	Current Lower Limb Paralysis	2	Trombocytopenia (<50 x 10 ⁹)	4
Trauma (<1 month)	5	Reduced Mobility	3	History of Cancer	1	Thrombophilia	2	Age >85yo	3.5
Spinal Cord Injury (<1 month)	5	Major Surgery or Trauma (≤1 month)	2			Age >60yo	1	Hepatic Failure (INR >1.5)	2.5
Age >75yo	3	Age >70yo	1			ICU/CCU	1	Renal Failure (GFR <30)	2.5
History of VTE	3	BMI ≥30	1			Immobilization ≥ 7 days	1	ICU/CCU	2.5
Family History of Thrombosis	3	Acute Heart/Respiratory Failure	1					Central Venous Access	2
Factor V Leiden	3	Acute Myocardial Infarction	1					Acute Rheumatic Disease	2
Prothrombin 20210A	3	Acute Infection/ Rheumatologic Disease	1					Current Cancer	2
Elevated Homocysteine	3	Hormone Therapy	1					Age 40-85	1.5
Lupus Anticoagulant	3							Male	1
Elevated Cardiolipin Antibody	3							Renal Failure (GFR 30-60)	1
Heparin-Induced Thrombocytopenia	3								
Congenital/Acquired Thrombophilia	3								
Age 64-75	2								
Arthroscopic Surgery	2								
Cancer	2								
Major Surgery (>45min)	2								
Laparoscopic Surgery (>45min)	2								
Immobilization (>72hrs)	2								
Plaster Cast	2								
Immobilization (>1mo)	2								
Central Venous Access	2								
Age 41-60yo	1								
Minor Surgery	1								
History of Prior Major Surgery (<1mo)	1								
Varicose Veins	1								
Inflammatory Bowel Disease	1								
Leg Swelling	1								
BMI >25	1								
Acute Myocardial Infarction	1								
Heart Failure Exacerbation (<1mo)	1								
Sepsis (<1mo)	1								
Acute Respiratory Disease (<1mo)	1								
Abnormal Pulmonary Function	1								
Active Bed Rest	1								
Ongoing Hormone Therapy	1								
Pregnant or Post-Partum (<1mo)	1								
Unexplained Stillborn or Recurrent Spontaneous Abortions	1								



Resources & Practical Tools

Eligibility Checklist for Post-Discharge VTE Prophylaxis

Consider prescribing **rivaroxaban 10 mg PO daily** for a total of 31-39 days (including inpatient days) for patients who meet the following criteria.

For patients aged >60 and hospitalized for ≥1 of the following acute medical conditions:

- Decompensated heart failure
- Respiratory insufficiency or COPD exacerbation
- Infectious or inflammatory disease
- Ischemic stroke with lower extremity paresis and reduced mobility

OR

For patients aged 40-59, hospitalized for ≥1 of the above acute medical illnesses

AND

Have ≥1 of the below additional VTE risk factor(s):

- Previous VTE or superficial vein thrombosis
- History of cancer
- History of NYHA Class III or IV heart failure
- Obesity (BMI >35)
- Inherited or acquired thrombophilia
- Current use of erythropoiesis-stimulating agent
- Current use of hormone therapy

Do not use if any of the following are present:

- Contraindications to anticoagulant prophylaxis
- Creatinine Clearance < 15 mL/min
- Concomitant combined P-gp and strong CYP3A4 inhibitors and inducers
- Pregnant or breastfeeding
- **Currently on dual antiplatelet therapy (DAPT)**
- **Active bleeding within the last 3 months**
- **Gastroduodenal ulcers within the last 3 months**
- **History of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage**
- **Active cancer (undergoing acute in-hospital cancer treatment)**

**Bolded exclusion criteria have been associated with increased fatal or major bleeding events*

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VTE Prophylaxis Order Set Build Specifications

VTE prophylaxis should be considered for patients considered high or moderate risk of VTE according to risk assessment tools. Patients considered low risk of VTE should not receive pharmacologic or mechanical VTE prophylaxis.



Disclaimers:

Heparin, enoxaparin and dalteparin recommendations do not apply to patients with acute or prior heparin-induced thrombocytopenia. Fondaparinux use should be considered in this population if clinically appropriate (clinically stable, no upcoming procedures, with creatinine clearance > 30 mL/min).

These recommendations do not apply to low body weight patients < 55 kg. Utilization of standard dose low molecular weight heparin and unfractionated heparin regimens in this population has been associated with increased bleeding events and/or supratherapeutic anti-Xa levels. Consider dose reduction in this population.

In Hospital Prophylaxis:

Creatinine clearance > 30 mL/min:

Normal weight:

- Enoxaparin 40 mg subcutaneously once daily (preferred)^a
- Dalteparin 5,000 units subcutaneously once daily (preferred)^a
- Unfractionated heparin 5,000 units subcutaneously q8h
- Rivaroxaban 10 mg orally once daily^c

Obesity (BMI > 40 kg/m² and weight > 100 kg):

- Enoxaparin 40 mg subcutaneously q12h (preferred)^{a,b}
- Dalteparin 7,500 units subcutaneously once daily (preferred)^a
- Unfractionated heparin 7,500 units subcutaneously q8h
- Rivaroxaban 10 mg orally once daily^c

Creatinine clearance 15-29 mL/min:

Normal weight:

- Unfractionated heparin 5,000 units subcutaneously q8h (preferred)
- Enoxaparin 30 mg subcutaneously once daily^a
- Dalteparin 5,000 units subcutaneously once daily^a
- Rivaroxaban 10 mg orally once daily^c

Obesity (BMI > 40 kg/m² and weight > 100 kg):

- Unfractionated heparin 7,500 units subcutaneously q8h
- Rivaroxaban 10 mg orally once daily^c

Creatinine clearance < 15 mL/min or renal replacement therapy:

Normal weight:

- Unfractionated heparin 5,000 units subcutaneously q8h

Obesity (BMI > 40 kg/m²)

- Unfractionated heparin 7,500 units subcutaneously q8h

Low body weight (weight < 50 kg):

- Unfractionated heparin 5,000 units subcutaneously q12h

^a Both enoxaparin and dalteparin will not be available on the formulary at most institutions. The formulary preferred low molecular weight heparin product should be included and non-formulary agents omitted during order set build.

^b Some experts recommend enoxaparin 0.5 mg/kg q12h for obese patients. Establish institutional standards when developing order sets.

^c Rivaroxaban is an option for extended prophylaxis in patients deemed to be at high risk for VTE and at low risk for bleeding. The total course of rivaroxaban (inpatient + outpatient) should be 31-39 days.