

# Extended Venous Thromboembolism Prophylaxis in Medically Ill Patients: An NATF Anticoagulation Action Initiative



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## ABSTRACT

Hospitalized patients with acute medical illnesses are at risk for venous thromboembolism (VTE) during and after a hospital stay. Risk factors include physical immobilization and underlying pathophysiologic processes that activate the coagulation pathway and are still present after discharge. Strategies for optimal pharmacologic VTE thromboprophylaxis are evolving, and recommendations for VTE prophylaxis can be further refined to protect high-risk patients after hospital discharge.

An early study of extended VTE prophylaxis with a parenteral agent in medically ill patients yielded inconclusive results with regard to efficacy and bleeding. In the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) trial, extended use of betrixaban halved symptomatic VTE, decreased hospital readmission, and reduced stroke and major adverse cardiovascular events compared with standard enoxaparin prophylaxis. Based on findings from APEX, the Food and Drug Administration approved betrixaban in 2017 for extended VTE prophylaxis in acute medically ill patients. In the Reducing Post-Discharge Venous Thrombo-Embolic Risk (MARINER) study, extended use of rivaroxaban halved symptomatic VTE in high-risk medical patients compared with placebo. In 2019, rivaroxaban was approved for extended thromboprophylaxis in high-risk medical patients, thus making available a new strategy for in-hospital and post-discharge VTE prevention.

To address the critical unmet need for VTE prophylaxis in medically ill patients at the time of hospital discharge, the North American Thrombosis Forum (NATF) is launching the Anticoagulation Action Initiative, a comprehensive consensus document that provides practical guidance and straightforward, patient-centered recommendations for VTE prevention during hospitalization and after discharge.

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## INTRODUCTION

We have reached a fork in the road for the prevention of venous thromboembolism (VTE) in patients who have been recently hospitalized and are medically ill. Approximately 1%-2% will develop symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) within 6 weeks of discharge after in-hospital VTE prophylaxis is terminated.<sup>1</sup> The rate of asymptomatic VTE during these 6 vulnerable weeks is more than 3 times higher than the rate of symptomatic events.<sup>2</sup> Some patients will be discharged to nursing home care, where VTE rates are up to 30-fold higher than in the general population and highest in the initial 7 days of admission.<sup>3</sup> In the United States, approximately 200,000 VTE events occur annually following discharge.<sup>4</sup> There is currently a disconnect among guideline recommendations, clinical trial data, and clinical practice.

An early study with low-molecular-weight heparin (LMWH) failed to show that the benefits of prophylactic extended-duration anticoagulation outweighed the risks when initiated during hospitalization and continued after discharge.<sup>5</sup> Conversely, in the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) trial, betrixaban reduced asymptomatic VTE, symptomatic VTE, stroke, death, and VTE-related rehospitalization within 30 days.<sup>6</sup> The Medically Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolic Risk (MARINER) trial then tested rivaroxaban against placebo in medically ill patients newly discharged from the hospital. Rivaroxaban halved the rate of symptomatic DVT and PE compared with placebo.<sup>7</sup>

The North American Thrombosis Forum (NATF) hereby presents a comprehensive Anticoagulation Action Initiative to help drive the appropriate use of VTE prophylaxis in medically ill patients. Developed by a panel of global experts, this consensus document explores the most recent data on extended-duration prophylaxis and serves as a contemporary guide for frontline providers and stakeholders, including hospitalists, internal medicine practitioners, pharmacists, nurse practitioners, physician assistants, subspecialty clinicians, and hematology, pulmonary medicine, and cardiovascular medicine staff.

## EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM IN HOSPITALIZED PATIENTS DURING STAY AND POST-DISCHARGE

### The Vulnerable Medically Ill Patient During Hospitalization and After Discharge

Hospitalized patients are vulnerable to the core elements of Virchow's triad that increase the risk of VTE:

hypercoagulability, venous stasis, and endothelial damage.<sup>8</sup> Patients are frequently bedbound during and after hospitalization for an acute medical illness. Following hospitalization, many patients continue to have limited mobility, along

with other conditions that lead to a hypercoagulable state (eg, prior VTE, elevated levels of procoagulant factors, and various comorbidities). Venous stasis is especially common in patients recovering from a heart failure or pneumonia hospitalization. Infectious and inflammatory conditions such as pneumonia or inflammatory bowel disease are associated with endothelial damage, a decrease in anticoagulant proteins S and C, and activation of platelets, all of which secrete inflammatory mediators that propagate additional thrombosis.

Nationwide studies estimate that approximately half of all hospitalized medical patients have 1 or more risk factors for VTE,<sup>9</sup> representing

more than 8 million Americans annually.<sup>10</sup> Among patients in the intensive care unit (ICU), hospital-associated VTE risk approaches 10%, even with appropriate prophylaxis.<sup>11</sup> However, the risk of VTE in the medical patient who is hospitalized is not just limited to the hospital period. In 1 nationwide claims-based analysis, hospital-associated symptomatic VTE rates varied between 1.28% over 90 days and 3.3% over 180 days.<sup>1,12</sup>

### The Critical Unrecognized and Unmet Need for Venous Thromboembolism Prevention During Hospitalization and After Discharge

Preventing hospital-acquired VTE has been the focus of multiple quality and regulatory efforts led by the Joint Commission,<sup>13</sup> the Centers for Medicare and Medicaid Services,<sup>14</sup> the Agency for Healthcare Research and Quality,<sup>15</sup> and the Surgeon General's Call to Action.<sup>16</sup> VTE is the most preventable hospital-associated complication, and implementation of appropriate prophylaxis is a requirement for institutional accreditation.

The 2008 Surgeon General's Call to Action for VTE prevention in patients who are hospitalized spurred accreditation metrics, hospital protocol changes, and new research to address this public health concern.<sup>16</sup> Many hospitals quickly moved to an "opt out" policy to give all hospitalized patients VTE prophylaxis unless contraindicated, in part to satisfy Joint Commission accreditation standards.

Several years ago, universal VTE prophylaxis was questioned as new data emerged. Validated VTE risk assessment models have shown that not all medically ill patients who are hospitalized are at high risk for developing VTE. However, 7 years later, many hospitals still have opt out policies.

## CLINICAL SIGNIFICANCE

- Patients with acute medical illnesses are at high risk for VTE during hospitalization and after discharge.
- Betrixaban reduced asymptomatic and symptomatic VTE in the APEX study. In the MARINER trial, rivaroxaban halved the rate of symptomatic VTE compared with placebo. Subsequently, the FDA approved these agents for extended VTE prophylaxis.
- Institution-wide initiatives to promote awareness around post-discharge VTE risk can help drive the appropriate use of prophylaxis in vulnerable patients.

We typically encounter 3 main categories of VTE risk in medically ill patients who are hospitalized:

- Those at low risk of VTE who do not require prophylaxis.
- Those at higher risk of VTE who should receive in-hospital, but not extended, prophylaxis.
- Those at very high risk of VTE who may be candidates for extended pharmacologic prophylaxis.

Interventions to reduce VTE risk include mechanical prophylactic means (such as pneumatic compression devices) and pharmacologic prophylaxis (anticoagulant drugs). Pharmacologic prophylaxis with heparin reduces the relative risk of VTE, but the reduction in absolute VTE rates is modest (~2-3 events per 1000 patients); heparin-based prophylaxis is also associated with an increased risk of bleeding.<sup>17,18</sup> Although some guidelines have advocated for “universal VTE prophylaxis” in medical patients, assessments of real-world practice have not supported this approach.<sup>12,19,20</sup> The heterogeneity in VTE risk among medical patients has subsequently led to a more nuanced risk-based approach where patients first undergo a risk assessment to determine optimal methods of VTE prophylaxis.

As the duration of acute-care hospital stays decreases, questions emerge about whether to extend VTE prophylaxis after discharge and, if so, for how long<sup>21,22</sup> because the underuse of prophylaxis places patients at an increased risk for preventable VTE.<sup>23-25</sup> Moreover, VTE prophylaxis is not always administered even when it is prescribed. Some reports have found that patients decline VTE prophylaxis 5%-13% of the time, potentially compromising treatment efficacy.<sup>26</sup> The need to inject anticoagulants (eg, unfractionated heparin and LMWH) may have been a key culprit for refusal of prophylaxis in the past. Presently, the use of oral agents (eg, betrixaban or rivaroxaban) may increase patient willingness to be anticoagulated.

Most quality initiatives have focused on the underuse of VTE prophylaxis, but emerging evidence suggests that overuse is also common and may contribute to an increased risk of adverse drug events, including bleeding, more patient inconvenience, and higher health care costs.<sup>27,28</sup> These ongoing challenges underscore the need for more effective and less burdensome strategies to risk stratify patients and individualize VTE prevention.

## RISK STRATIFICATION TOOLS AND POPULATION MANAGEMENT

Over the past 2 decades, risk assessment models (RAMs) have been developed to help clinicians identify patients at high risk for VTE and assess the appropriateness of VTE prophylaxis. These models differ from those used to clinically diagnose VTE, such as the Wells Criteria for DVT<sup>29</sup> and PE.<sup>30</sup>

Qualitative RAMs, such as the 3-bucket model (Table 1), stratify patients by VTE risk categories (ie, low, medium, and high) to determine the need for prophylaxis. Although these models are user-friendly, there is concern that they may oversimplify risk and set a low threshold for anticoagulation.

**Table 1** Updated “3-Bucket” Model

### Low-Risk Patients

- Patients under observation with expected stay <48 hours
- Ambulatory medical patients
- Minor ambulatory surgery patients without strong risk factors
- Ambulatory cancer patients in hospital for short chemotherapy infusion

### Moderate-Risk Patients

- Majority of general surgical patients
- Medical patients with decrease in ambulation **AND** VTE risk factors, including congestive heart failure, myocardial infarction, stroke, pneumonia, active inflammation, or age >65
- Active cancer diagnosis, past VTE, or known thrombophilia in medical patients with hospital LOS >48 hours

### High-Risk Patients

- Patients undergoing major surgery, knee or hip arthroplasty, hip fracture repair, major neurosurgery, or abdominal-pelvic surgery for cancer
- Patients with major trauma

VTE = venous thromboembolism; LOS = length of stay.

Quantitative models weigh multiple VTE risk factors to generate point-based risk scores; several have been externally validated (Table 2). Although such models embody a more individualized risk approach, they are complex in nature and can be time-consuming and difficult to implement.

The Padua Prediction Score<sup>31</sup> is a simple scoring system to risk stratify medically ill patients admitted to a general medicine floor. Scores  $\geq 4$  indicate high risk for VTE; scores <4 denote a low risk. Of note, this score does not consider hemorrhagic risk and has not been validated in specific populations (eg, patients in the ICU).

The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE), an observational study, led to the creation of the IMPROVE<sup>32</sup> score to assess VTE risk in medically ill patients who are hospitalized. There are 2 versions of IMPROVE: the 4-factor predictive score includes independent VTE risk factors present at admission, while the 7-factor associative score includes risk factors prior to admission and during hospitalization. The IMPROVEDD<sup>33</sup> score adds D-dimer as an additional risk factor in the 7-factor model. Risk factors are weighted with 1-3 points each, with higher scores indicating higher risk for VTE. Patients with a score  $\geq 2$  should receive in-hospital VTE prophylaxis, whereas patients with a score  $\geq 4$  may qualify for extended post-discharge prophylaxis (up to 45 days).<sup>34</sup>

The Khorana Risk Score<sup>35</sup> was developed to predict risk for VTE in ambulatory patients with cancer undergoing chemotherapy. Patients are categorized into low-risk (score 0), intermediate-risk (score 1-2), and high-risk (score  $\geq 3$ ) groups. Studies have found that risk for VTE in patients with cancer closely parallels the risk of mortality.<sup>36,37</sup> This model has been widely validated.<sup>38,39</sup>

The Caprini VTE score<sup>40,41</sup> is a validated tool used to assess VTE risk in patients who are undergoing, or have recently had, surgery.<sup>42-44</sup> In-hospital chemoprophylaxis is

**Table 2** Validated Venous Thromboembolism Risk Assessment Models With Variables

Score	Padua	IMPROVE	GENEVA (revised)	Caprini	Kucher	Khorana	Intermountain
Patient Population	Acutely ill hospitalized medical patients			Medical and surgical patients		Cancer patients	Patients previously diagnosed with VTE
Weighted Variables	11	7	8	39	8	5	4
Complexity							
Risk Factors (5 points each)	Not applicable	Not applicable	Heart rate $\geq 95$	<ul style="list-style-type: none"> <li>• Elective major lower extremity arthroplasty</li> <li>• Hip, pelvis, or leg fracture (&lt;1 month)</li> </ul>	Not applicable		
Risk Factors (4 points each)	Not applicable	Not applicable	Pain on lower limb palpation and unilateral edema	<ul style="list-style-type: none"> <li>• Stroke (&lt;1 month)</li> <li>• Trauma (&lt;1 month)</li> <li>• Acute spinal cord injury (paralysis; &lt;1 month)</li> <li>• Major surgery lasting longer than 3 hours</li> </ul>			
Risk Factors (3 points each)	<ul style="list-style-type: none"> <li>• Active cancer</li> <li>• Previous VTE (excluding superficial thrombosis)</li> <li>• Reduced mobility</li> <li>• Known thrombophilic condition</li> </ul>	<ul style="list-style-type: none"> <li>• Previous VTE</li> <li>• Known thrombophilia</li> </ul>	<ul style="list-style-type: none"> <li>• Previous VTE</li> <li>• Unilateral lower limb pain</li> <li>• Heart rate 75-94</li> </ul>	<ul style="list-style-type: none"> <li>• Age &gt;75 years</li> <li>• Major surgery lasting 2-3 hours</li> <li>• BMI &gt;50 (venous stasis syndrome)</li> <li>• History of SVT, DVT/PE</li> <li>• Family history of DVT/PE</li> <li>• Present cancer or chemotherapy</li> <li>• Positive Factor V Leiden</li> <li>• Positive prothrombin 20210A</li> <li>• Elevated serum homocysteine</li> <li>• Positive lupus anticoagulant</li> <li>• Elevated anticardiolipin antibodies</li> <li>• Heparin-induced thrombocytopenia</li> <li>• Other thrombophilia</li> </ul>	<ul style="list-style-type: none"> <li>• Active cancer</li> <li>• Previous VTE (excluding superficial thrombosis)</li> <li>• Already known thrombophilic condition/hypercoagulability</li> </ul>	Not applicable	<ul style="list-style-type: none"> <li>• Bed rest</li> <li>• Peripherally inserted central venous catheterization line</li> <li>• Cancer</li> </ul>
Risk Factors (2 points each)	<ul style="list-style-type: none"> <li>• Recent (&lt;1 month) trauma or surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Current lower limb paralysis</li> </ul>	<ul style="list-style-type: none"> <li>• Surgery or lower limb fracture in past month</li> <li>• Active malignancy</li> <li>• Hemoptysis</li> </ul>	<ul style="list-style-type: none"> <li>• Age 60-74 years</li> <li>• Major surgery (&gt;60 minutes)</li> <li>• Arthroscopic surgery (&gt;60 minutes)</li> <li>• Laparoscopic surgery (&gt;60 minutes)</li> <li>• Previous malignancy</li> <li>• Central venous access</li> <li>• Morbid obesity (BMI &gt;40)</li> </ul>	<ul style="list-style-type: none"> <li>• Major surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Cancer type <ul style="list-style-type: none"> <li>- Stomach</li> <li>- Pancreas</li> </ul> </li> </ul>	
Risk Factors (1 Point each)	<ul style="list-style-type: none"> <li>• Elderly age (&gt;70 years)</li> <li>• Heart or respiratory failure</li> <li>• Acute myocardial infarction or stroke</li> <li>• Acute infection and/or rheumatologic disorder</li> <li>• Obesity (BMI &gt;30)</li> <li>• Ongoing hormonal treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Cancer</li> <li>• Age &gt;60 years</li> <li>• Immobility &gt;7 days</li> <li>• ICU/CCU stay</li> </ul>	<ul style="list-style-type: none"> <li>• Age &gt;65 years</li> </ul>	<ul style="list-style-type: none"> <li>• Age 41-60 years</li> <li>• Minor surgery planned</li> <li>• History of prior major surgery</li> <li>• History of inflammatory bowel disease</li> <li>• Swollen legs (current)</li> <li>• Varicose veins</li> <li>• Obesity (BMI &gt;30)</li> <li>• Acute myocardial infarction (&lt;1 month)</li> <li>• Congestive heart failure (&lt;1 month)</li> <li>• Sepsis (&lt;1 month)</li> <li>• Serious lung disease including pneumonia (&lt;1 month)</li> <li>• Abnormal pulmonary function (COPD)</li> <li>• Medical patient currently at bed rest</li> <li>• Leg plaster cast or brace</li> <li>• Oral contraceptives or hormone replacement therapy</li> <li>• Pregnancy or postpartum (&lt;1 month)</li> <li>• History of unexplained stillborn infant, recurrent spontaneous abortion (&gt;3), premature birth with toxemia or growth-restricted infant</li> </ul>	<ul style="list-style-type: none"> <li>• Age &gt;70 years</li> <li>• Obesity (BMI &gt;30)</li> <li>• Bed rest/immobility</li> <li>• Ongoing hormone treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Cancer type <ul style="list-style-type: none"> <li>- Lung</li> <li>- Lymphoma</li> <li>- Gynecologic</li> <li>- Bladder</li> <li>- Testicular</li> </ul> </li> <li>• Prechemotherapy platelet count &gt;350 <math>\times</math> 109/L</li> <li>• Hemoglobin level &lt;10 g/dL or using RBC growth factors</li> <li>• Prechemotherapy leukocyte count &gt;11 <math>\times</math> 109/L</li> <li>• BMI &gt;35 kg/m<sup>2</sup></li> </ul>	

**Table 2 (Continued)**

Score	Padua Acutely ill hospitalized medical patients	IMPROVE	GENEVA (revised)	Caprini Medical and surgical patients	Kucher	Khorana Cancer patients	Intermountain Patients previously diagnosed with VTE
Weighted Variables	11	7	8	39	8	5	4
Risk Stratification Scores	High risk: $\geq 4$	High risk: $\geq 2$	Low risk: 0-3 Moderate risk: 4-10 High risk: $> 10$	Low risk: 0-1 Moderate risk: 2 High risk: 3-4 Super high risk: $> 5$	High risk: $> 4$	High risk: $\geq 2$	High risk: $> 1$
Strengths and Limitations	Able to discriminate between high/low risk of VTE medical patients Has not been validated and use cannot be supported	Validated score widely used Limited target population	Favorable comparison with Padua Can accurately identify low-risk patients who do not require thromboprophylaxis Intended to guide workup and testing by predicting pretest probability of PE, but not for diagnosis	More weighted variables compared to Padua score Application in specific medical patients is not determined Generally recommended for use in surgical patients	Designed to define a known high-risk population for targeted computerized alerts Not a sensitive instrument to capture all patients at risk	Cancer-validated score Inpatient or ambulatory application Can be used even during chemotherapy	Simple form Institution-specific

BMI = body mass index; CCU = critical care unit; COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; ICU = intensive care unit; PE = pulmonary embolism; RBC = red blood cell; SVT = superficial venous thrombosis; VTE = venous thromboembolism.

recommended for patients with moderate risk (score 3-4), and prolonged prophylaxis for 7-10 days is endorsed for those at high risk (score 5-8). Patients in the highest-risk group (score  $\geq 8$ ) should receive extended prophylaxis for 30 days. Several studies are exploring the utility of the Caprini score in medically ill patients and those with cancer.<sup>45,46</sup>

The Kucher model is an 8-factor weighted scoring system that uses computer alerts to identify high-risk populations (scores  $\geq 4$  points indicate high risk). In a randomized controlled trial, symptomatic VTE rates declined by 41% in high-risk patients after alerts were sent to providers. This model has been used as an embedded RAM in order sets at Brigham and Women's Hospital.<sup>47,48</sup>

The Intermountain model identifies patients at risk for VTE within 90 days and offers a simple, clinically driven, and easy-to-implement approach during hospitalization. The model was developed in part by using the International Classification of Diseases-Ninth Revision (ICD-9) codes from electronic medical records to determine prevalent VTE risk factors among patients who are hospitalized and includes 4 highly predictive factors for VTE: a peripherally inserted central catheter, a clinical order for bedrest, previous history of VTE, and cancer diagnosis. Although cancer is identified as a VTE risk factor in this RAM, it has not been shown to be the most predictive risk factor. ICD codes are routinely used to classify cancer as a VTE risk factor, but they do not indicate whether a patient's cancer is active. This limitation may explain the reduced predictive ability of a cancer diagnosis during hospitalization, compared with cancer as a risk factor before hospitalization.<sup>48,49</sup>

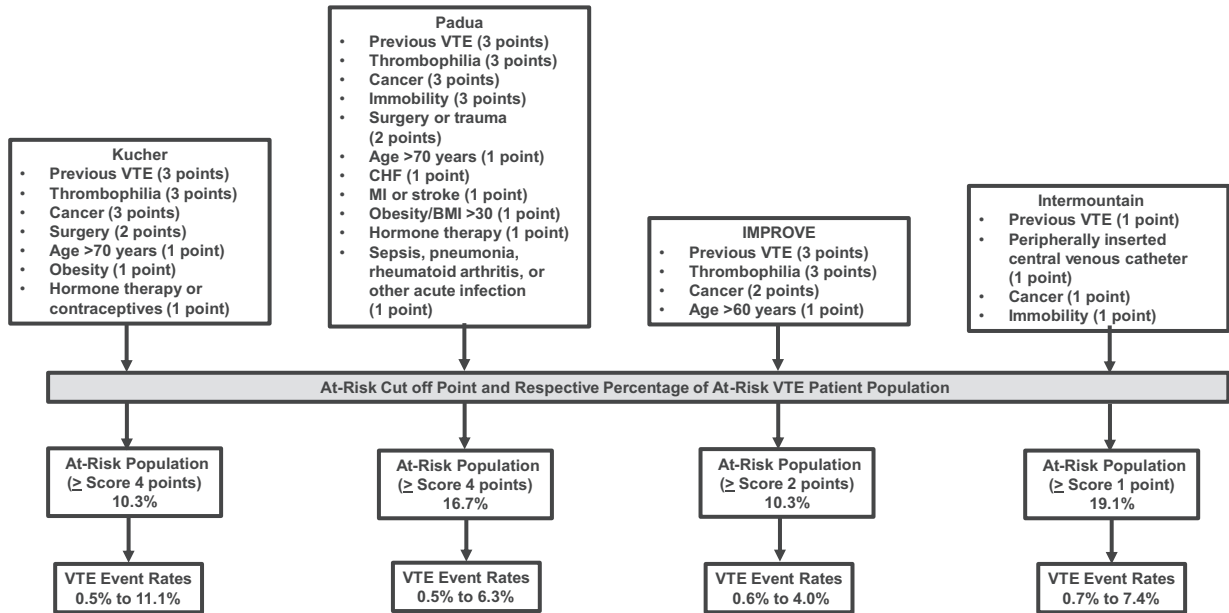
The Geneva risk score is based on inclusion criteria from several VTE prevention trials and on recommendations from the American College of Chest Physicians (ACCP) guidelines. This score assigns 1-2 points to a variety of VTE risk factors and has the benefit of being modeled on risk factors that were included in randomized controlled trials. A Geneva risk score of  $\geq 3$  indicates high risk, whereas patients with a score  $< 3$  are considered low risk. When compared with the Padua score, the Geneva score had better sensitivity (90.0% vs 73.3%) and specificity (99.4% vs 98.9%) in predicting which patients would develop VTE.<sup>50</sup>

In a validation study of 4 quantitative RAMs within the Michigan Hospital Medicine Safety Consortium Cohort (Figure 1),<sup>51</sup> 10%-20% of medical patients who were acutely ill and hospitalized were classified as having a high risk for VTE.

### EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

Protocols for VTE prophylaxis in at-risk hospitalized patients are well-established, whereas attempts to extend prophylaxis after discharge have been met with mixed results. At present, there have been 5 clinical trials of extended prophylaxis in hospitalized medical patients with either LMWH or factor Xa inhibitors (Table 3 and Figure 2).

## Risk Assessment Models, Risk Factor Points Score, At-Risk Population, and VTE Event Rates



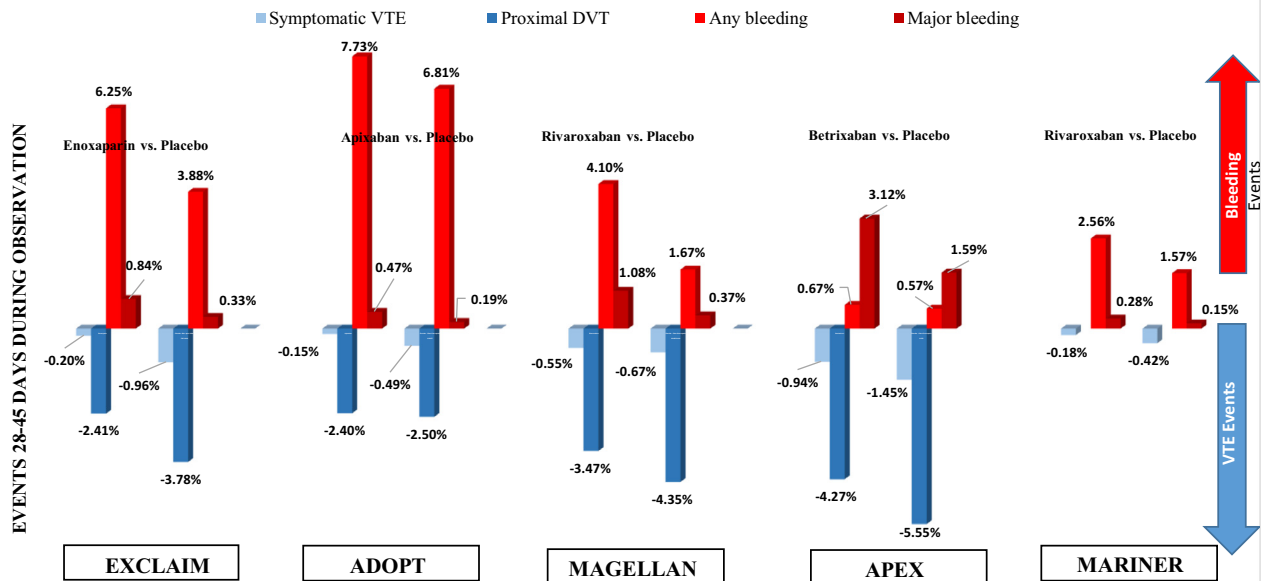
**Figure 1** The Michigan Hospital Medicine Safety Consortium cohort.

### Enoxaparin

The first trial to investigate the efficacy and safety of extended VTE prophylaxis in acutely ill medical patients was the Extended VTE Prophylaxis in Acutely Ill Medical

Patients with Prolonged Immobilization (EXCLAIM) trial, which randomized 5963 patients.<sup>5</sup> Eligible patients were ≥40 years of age, hospitalized for an acute medical illness, had reduced mobility for ≥3 days before study enrollment,

## Comparison of the Efficacy and Safety of Extended VTE Prophylaxis in Medically Ill Patients



Results are shown in percent of patients (the y-axis group). On the x-axis, all patients are compared by treatment arm in each study. Treated patients are analyzed with regards to total events divided by total exposed patients during study.

**Figure 2** Extended venous thromboembolism (VTE) in studies of medically ill patients: comparative efficacy and safety. ARR = absolute risk reduction.

**Table 3** Comparison of Extended Venous Thromboembolism Thromboprophylaxis Landmark Trials

	Trial EXCLAIM	ADOPT	APEX	MAGELLAN	MARINER
Criteria					
<b>N</b>	5963	6528	7513	8101	12,024
Age	At least 40 years of age	At least 40 years of age	Age $\geq$ 40 years	Age $\geq$ 40 years	Age $\geq$ 40 years
Presentation	Hospitalized for an acute medical illness (heart failure, respiratory insufficiency, or infection)	Congestive heart failure, acute respiratory failure with infection (without septic shock), acute rheumatic disorder, inflammatory bowel disease	At least 1 of the following as the cause of acute hospitalization: acute decompensated heart failure with prior symptomatic chronic heart failure; acute respiratory failure in patients with chronic symptomatic lung disease; acute infection without septic shock (eg, with systolic blood pressure $<$ 90 mm Hg after fluid challenge that requires pressor therapy) at screening and randomization; acute rheumatic disorders including acute lumbar pain, sciatica, vertebral compression, rheumatoid arthritis, systemic lupus erythematosus, etc.; acute ischemic stroke with lower extremity hemiparesis or hemiparalysis	Patients at risk of VTE events being hospitalized for acute medical conditions such as heart failure (NYHA class III or IV), active cancer (eg, admitted for chemotherapy or for treatment of a complication of the active cancer), acute ischemic stroke (documented) with leg paresis or paralysis and inability to walk without assistance, acute infection, acute respiratory insufficiency, acute rheumatic disorders, acute inflammatory bowel disease, diabetes mellitus (eg, diabetic ketoacidosis, hyperosmolar coma), pancreatitis (surgical management not planned), cholecystitis (surgical management not planned), other	The reason for the index hospitalization must have been a new diagnosis or exacerbation of one of the following medical conditions: heart failure, acute respiratory insufficiency or acute exacerbation of COPD, acute ischemic stroke (including spinal cord infarction if no evidence of intramedullary, subdural or epidural hemorrhage), acute infectious disease, or inflammatory disease, including rheumatic disease
Additional Presentation Factors	Age $>$ 75 years, history of VTE, or active or previous cancer	Age $\geq$ 75, previously documented VTE or history of VTE and anticoagulation treatment for at least 6 weeks, cancer, BMI $\geq$ 30, estrogenic hormone therapy, chronic heart or respiratory failure	Any of the following: $\geq$ 75 years of age; 60-74 years of age with D-dimer $\geq$ 2x ULN; 40-59 years of age with D-dimer $\geq$ 2x ULN and a history of either VTE (DVT or PE) or cancer (excluding nonmelanoma carcinoma of the skin)	N/A	Total modified IMPROVE VTE risk score is $\geq$ 4, or if the total modified IMPROVE VTE risk score is 2 or 3 with a D-dimer $>$ 2x ULN

Table 3 (Continued)

	Trial EXCLAIM	ADOPT	APEX	MAGELLAN	MARINER
Hospitalization		Expected hospitalization of $\geq 3$ days after randomization	Expected total length of current hospitalization $\geq 3$ days, enrollment occurs $< 96$ hours after hospitalization/presentation (eg, in emergency department) for acute medical illness	Hospitalized $< 48$ hours before randomization	The duration of the index hospitalization must have been at least 3—but no more than 10—consecutive days
Mobility	Reduced mobility for $\geq 3$ days before enrollment and likely to have reduced mobility for $\geq 3$ days after enrollment	Severely or moderately restricted mobility	Severely immobilized for 24 hours or anticipated to be severely immobilized for 24 hours (severely immobilized means patients are confined to a bed or chair for most the day and can only be independently mobile to the in-room toilet. In-bed/chair physical therapy is permitted, after 24 hours of severe immobilization; patients are anticipated to be severely or moderately immobilized for 3 or more days. Moderately immobilized means patients can be independently mobile to the in-room or ward toilet; can be mobilized by physical therapy or nursing staff; and can be off-ward with assistance)	Anticipated complete immobilization during the first day of hospitalization and anticipated decreased level of mobility (bed rest) plus hospital stay duration of at least 4 days	Complete immobilization of $\geq 1$ day is associated with an IMPROVE VTE risk score of 1
Drug Dose and Duration	All patients received open-label SC enoxaparin 40 mg once daily for $10 \pm 4$ days and were then randomized in a double-blind fashion to SC enoxaparin or placebo for $28 \pm 4$ days	Patients randomized to SC enoxaparin once daily for duration of hospital stay ( $\geq 6$ days) or to apixaban 2.5 mg twice daily for 30 days	Patients randomized to enoxaparin 40 mg SC once daily for $10 \pm 4$ days and then oral placebo once daily, or a betrixaban loading dose of 160 mg followed by 80 mg once daily for 35-42 days Patients with creatinine clearance of 15-30 mL/min received half-dose enoxaparin (20 mg) and betrixaban (an 80-mg loading dose followed by a 40-mg maintenance dose) Patients receiving concomitant strong P-glycoprotein (P-gp) inhibitors also received dose reduction for betrixaban	Patients randomized to either enoxaparin 40 mg SC once daily for $10 \pm 4$ days plus oral placebo or to an identical enoxaparin regimen plus rivaroxaban 10 mg once daily for $35 \pm 4$ days	At hospital discharge, patients randomized to rivaroxaban 10 mg once daily (dose reduction to 7.5 mg if creatinine clearance 30-50 mL/min) or to placebo for 45 days

BMI = body mass index; COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; NYHA = New York Heart Association; PE = pulmonary embolism; SC = subcutaneous; VTE = venous thromboembolism.



and had a high likelihood of reduced mobility for  $\geq 3$  days after enrollment. All patients received open-label subcutaneous enoxaparin 40 mg once daily for  $10 \pm 4$  days and were then randomized in a double-blind fashion to subcutaneous enoxaparin or placebo for  $28 \pm 4$  days. The primary efficacy endpoint was a composite of symptomatic or asymptomatic proximal DVT and symptomatic or fatal PE. The primary safety endpoint was modified International Society on Thrombosis and Haemostasis (ISTH) major bleeding. Patients received open-label enoxaparin for a median of 8 days and randomized therapy for a median of 27 days. Patients who received extended prophylaxis with enoxaparin demonstrated a 37% reduction in the primary efficacy endpoint compared with placebo (2.5% vs 4.0%,  $P < 0.003$ ), which was offset by an increase in major bleeding (0.7% vs 0.2%,  $P = 0.02$ ).

### Apixaban

The Study of Apixaban for the Prevention of Thrombosis-related Events in Patients with Acute Medical Illness (ADOPT) trial assessed the use of apixaban for extended prophylaxis.<sup>52</sup> Inclusion criteria were age  $\geq 40$  years, acute medical illness with an expected hospital stay  $\geq 3$  days, and moderate or severe restricted mobility. (Patients without heart or respiratory failure who had at least 1 additional risk factor were classified as having an “acute medical illness.”) There were 6528 patients randomized to subcutaneous enoxaparin once daily for the duration of their hospital stay ( $\geq 6$  days) or apixaban 2.5 mg twice daily for 30 days. The primary efficacy endpoint was a composite of symptomatic DVT, asymptomatic proximal DVT, symptomatic PE, or VTE-related death. The primary safety endpoint was ISTH major or clinically relevant nonmajor bleeding. At 30 days, apixaban was associated with a nonsignificant 13% reduction in the primary efficacy endpoint compared with enoxaparin (2.7% vs 3.1%,  $P = 0.44$ ). There was a nonsignificant increase in major or clinically relevant nonmajor bleeding but a significant excess in major bleeding (0.5% vs 0.2%,  $P = 0.04$ ).

### Rivaroxaban

There have been 2 randomized, double-blind, double-dummy trials investigating rivaroxaban for extended prophylaxis. The first was 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.<sup>53</sup> Eligible patients were randomized to either enoxaparin 40 mg subcutaneous once daily for  $10 \pm 4$  days plus oral placebo or to an identical enoxaparin regimen plus rivaroxaban 10 mg once daily for  $35 \pm 4$  days. Eligibility criteria included age  $\geq 40$  years, hospitalization for an acute medical illness  $< 72$  hours prior to randomization, reduced mobility, and anticipated ongoing decreased mobility. The primary efficacy endpoint—a composite of symptomatic DVT, asymptomatic proximal DVT,

symptomatic PE, or VTE-related death—was assessed in 8101 patients, with evaluation for non-inferiority at day 10 and superiority at day 35. The primary safety endpoint was ISTH major or clinically relevant nonmajor bleeding. Non-inferiority was met for efficacy at day 10 (2.7% in both groups,  $P_{\text{non-inferiority}} = 0.003$ ). There was a 23% reduction in the primary endpoint at 30 days with rivaroxaban compared with placebo (4.4% vs 5.7%,  $P = 0.02$ ). However, there was an increase in major (1.1% vs 0.4%,  $P < 0.001$ ) and clinically relevant nonmajor bleeding (4.1% vs 1.7%,  $P < 0.001$ ) at day 35.

The MARINER trial was the second large-scale study to investigate the use of rivaroxaban for extended prophylaxis and identified patients at a higher risk.<sup>7</sup> Patients were eligible if they were  $\geq 40$  years of age and had been hospitalized for at least 3 days but not more than 10 consecutive days, with 1 of the following conditions: heart failure with left ventricular dysfunction (ejection fraction  $\leq 45\%$ ), acute respiratory insufficiency or exacerbation of chronic obstructive pulmonary disease, acute ischemic stroke, or acute infectious or inflammatory disease, including rheumatic diseases. Patients also had to have additional VTE risk factors, as indicated by a modified IMPROVE score of  $\geq 4$ , or a score of 2-3 plus a plasma D-dimer level  $\geq 2 \times$  the upper limit of normal (ULN). There were 12,024 patients randomized at hospital discharge to rivaroxaban 10 mg once daily (dose reduction to 7.5 mg if creatinine clearance 30-50 mL/min) or to placebo for 45 days. The primary efficacy endpoint was a composite of symptomatic VTE or death resulting from VTE. Asymptomatic patients did not undergo venous ultrasound examination of the legs. The primary safety endpoint was major bleeding. Rivaroxaban was associated with a nonsignificant 24% reduction in the primary efficacy endpoint compared with placebo (0.83% vs 1.10%,  $P = 0.14$ ) and a nonsignificant increase in major bleeding (0.28% vs 0.15%, hazard ratio [HR] 1.88; 95% confidence interval [CI], 0.84-4.23). However, rivaroxaban halved symptomatic VTE events when compared with placebo (0.18% vs 0.42%, HR 0.44; 95% CI, 0.22- 0.89) but also resulted in a 67% increase in clinically relevant nonmajor bleeding (1.42% vs 0.85%, HR 1.66; 95% CI, 1.17-2.35).

Based on the results from the MAGELLAN and MARINER studies, the Food and Drug Administration (FDA) gave rivaroxaban a new indication for VTE prophylaxis in 2019. The approval was granted for prevention of VTE and VTE-related death in acute medically ill patients who were hospitalized and at risk for VTE complications but not at high risk of bleeding. Rivaroxaban can now be initiated in these patients during hospitalization and after discharge for a total recommended duration of 31-39 days.

### Betrixaban

The double-blind, double-dummy APEX trial assessed the use of betrixaban for extended VTE prophylaxis.<sup>6</sup> Initial eligibility criteria included age  $\geq 40$  years, hospitalization for an acute medical illness, an anticipated hospital length

of stay  $\geq 3$  days, anticipation of severe immobility  $\geq 24$  hours, and either severe or moderate immobility for  $\geq 3$  days. Patients were also required to have at least 1 additional baseline factor associated with an increased risk of VTE: D-dimer concentration  $\geq 2 \times$  ULN, age  $\geq 75$  years, or  $\geq 2$  additional VTE risk factors. Based on guidance from the FDA, the original study enrollment criteria were modified to include hospitalization for an acute medical illness, anticipated moderate or severe immobility for  $\geq 24$  hours, and 1 of the following: age  $\geq 75$  years, age 60-74 years with a D-dimer concentration  $\geq 2 \times$  ULN, or age 40-59 years with  $\geq 2 \times$  ULN plus a history of prior VTE or cancer. These modified criteria identified 3 prespecified risk cohorts for analysis: cohort 1 (primary analysis cohort, that is, patients with D-dimer concentration  $\geq 2 \times$  ULN); cohort 2 (all patients from cohort 1 plus patients  $\geq 75$  years of age), and cohort 3 (overall efficacy population, that is, all patients in cohort 1 and 2 and other patients who met the inclusion criteria). There were 7513 patients randomized to enoxaparin 40 mg subcutaneous once daily for  $10 \pm 4$  days and then oral placebo once daily, or a betrixaban loading dose of 160 mg followed by 80 mg once daily for 35-42 days. Patients with a creatinine clearance of 15-30 mL/min received half-dose enoxaparin (20 mg) and betrixaban (an 80-mg loading dose followed by a 40-mg maintenance dose). Patients receiving concomitant strong P-glycoprotein (P-gp) inhibitors also received dose reduction for betrixaban. The primary efficacy endpoint was a composite of symptomatic DVT, asymptomatic proximal DVT, symptomatic PE, or VTE-related death at the end of betrixaban therapy (35-42 days). The primary safety endpoint was ISTH major bleeding.

In the primary analysis group (cohort 1), extended-duration betrixaban had a 19% reduction in the primary efficacy endpoint (6.9% vs 8.5%,  $P = 0.054$ ). There was a 20% reduction (5.6% vs 7.1%,  $P = 0.03$ ) observed in cohort 2 and a 24% reduction (5.3% vs 7.0%,  $P = 0.006$ ) in cohort 3, although these results were considered exploratory as secondary endpoints. Most of the events prevented were asymptomatic proximal DVT; however, there was a significant 35% reduction in symptomatic VTE with betrixaban in cohort 3 (0.9% vs 1.5%, relative risk [RR] 0.64; 95% CI, 0.42-0.98), with an absolute risk reduction that was more sizable than that seen in MAGELLAN for rivaroxaban (0.6% vs 0.2%).

Unlike the other extended-duration trials, betrixaban was not associated with excess major bleeding (cohort 1: 0.6% vs 0.7%,  $P = 0.72$ ; cohort 2: 0.7% vs 0.6%,  $P = 0.56$ ; cohort 3: 0.7% vs 0.6%,  $P = 0.55$ ), but there was an approximately 2-fold excess in clinically relevant nonmajor bleeding (cohort 1: 3.1% vs 1.9%,  $P = 0.009$ ; cohort 2: 3.2% vs 1.7%,  $P < 0.001$ ; cohort 3: 3.1% vs 1.6%,  $P < 0.001$ ).

The APEX investigators have published important substudies. Dose reduction of betrixaban, implemented to achieve similar drug concentrations in patients with severe renal insufficiency taking potent P-gp inhibitors, appears to attenuate the benefit.<sup>54</sup> A post hoc analysis of APEX found that betrixaban reduced fatal and irreversible events and that

reductions in these “hard” endpoints continued after study drug discontinuation, suggesting a legacy effect of betrixaban on these outcomes.<sup>55</sup> For example, extended prophylaxis with betrixaban resulted in a 47% reduction in ischemic stroke at day 77 (0.48% vs 0.91%,  $P = 0.026$ ), primarily driven by a benefit in patients who entered the trial with ischemic stroke or heart failure.<sup>56</sup> Based on these cumulative data, the FDA approved betrixaban in 2017 for extended-duration VTE prophylaxis in patients hospitalized for an acute medical illness who are at risk for VTE complications as a result of moderate or severe restricted mobility and other VTE risk factors. Further publications and subgroup analyses from APEX showed favorable treatment effects across multiple subpopulations and clinical outcomes (Table 4).

### Meta-Analysis: MARINER, APEX, MAGELLAN, ADOPT, and EXCLAIM

A recent meta-analysis<sup>57</sup> of these 5 randomized trials showed that extended-duration thromboprophylaxis reduced symptomatic VTE or VTE-related death compared with routine care (0.8% vs 1.2%,  $P = 0.002$ ) but increased ISTH major or fatal bleeding (0.6% vs 0.3%,  $P < 0.001$ ). The analysis showed that the pooled number needed to prevent 1 symptomatic VTE or VTE-related death was 250, whereas the number needed to cause 1 major or fatal bleeding event was 333. The authors advocate for the development of pathways to implement post-discharge thromboprophylaxis.

### CURRENT PRACTICE RECOMMENDATIONS AND GUIDELINES

Guidance around VTE risk assessment and prophylaxis varies across different societies and organizations. The ISTH Steering Committee for World Thrombosis Day has called for VTE risk assessment in all patients who are hospitalized.<sup>58</sup> The American College of Physicians (ACP) recommends assessment of VTE and bleeding risk prior to prophylaxis initiation.<sup>19</sup> The American College of Chest Physicians (ACCP) recommends against 1) pharmacologic or mechanical VTE prophylaxis in acute medically ill patients with a low risk for VTE and 2) pharmacologic prophylaxis in patients who are bleeding or have a high bleeding risk. They do recommend mechanical prophylaxis if bleeding risk is high, with transition to pharmacologic methods when bleeding risk abates (if VTE risk remains high).<sup>59</sup> These guidelines were developed before data from MARINER and APEX were available.

The 2018 American Society of Hematology (ASH) guidelines for VTE management do not recommend the routine use of extended VTE prophylaxis in acutely ill medical inpatients at this time (strong recommendation, moderate certainty). This recommendation was based on an internal meta-analysis that included data available at the time of guideline development in 2017. The analysis found that the reduction in VTE events with extended post-hospital prophylaxis was similar to the number of bleeding

**Table 4** APEX Post Hoc Analysis

Topic	Title	Most Important Takeaway Finding	Reference	DOI
Design Paper	The Design and Rationale for the Acute Medically Ill Venous Thromboembolism Prevention with Extended Duration Betrixaban (APEX) Study.	Previous trials of extended prophylaxis have identified the patients at risk of VTE in the medically ill population. The APEX trial tested two hypotheses: 1) betrixaban is a safe and efficacious drug for VTE prophylaxis, and 2) an extended duration of prophylaxis in high-risk patients improves the outcomes over the current standard of care.	<i>Am Heart J.</i> 2014 Mar;167(3):335-41.	10.1016/j.ahj.2013.11.006
Primary Results	Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients.	Among acutely ill medical patients with an elevated D- dimer level, there was no significant difference between extended-duration betrixaban and a standard regimen of enoxaparin in the VTE composite (6.9% vs 8.5%; RR = 0.81 [0.65-1.00]; $P = 0.054$ ) or major bleeding (0.6% vs 0.7%; RR = 0.88 [0.44-1.76]; $P = 0.72$ ). Exploratory analyses provided evidence suggesting a benefit for betrixaban in cohort 2 (age $\geq 75$ years or D- dimer) (5.6% vs 7.1%; RR = 0.80 [0.66-0.98]; $P = 0.03$ ) and overall population (5.3% vs 7.0%; RR = 0.76 [0.63-0.92]; $P = 0.006$ ).	<i>N Engl J Med.</i> 2016 Aug 11;375(6):534-44.	10.1056/NEJMoa1601747
Stroke	Extended-Duration Betrixaban Reduces the Risk of Stroke Versus Standard-Dose Enoxaparin Among Hospitalized Medically Ill Patients: An APEX Trial Substudy (Acute Medically Ill Venous Thromboembolism Prevention With Extended Duration Betrixaban).	There were fewer all-cause strokes (0.54% vs 0.97%; RR = 0.56 [0.32-0.96]; $P = 0.032$ ) and ischemic strokes (0.48% vs 0.91%; RR = 0.53 [0.30-0.94]; $P = 0.026$ ) among patients treated with betrixaban vs enoxaparin through 77 days of follow-up. Among acutely ill hospitalized patients, the short-term stroke risk was unexpected high (reviewed in <i>Expert Rev Hematol.</i> 2017 Aug;10(8):679-684) and the study explored the effect of betrixaban in stroke prevention.	<i>Circulation.</i> 2017 Feb 14;135(7):648-655.	10.1161/CIRCULATIONAHA.116.025427
Full vs Reduced Dose	The Safety and Efficacy of Full- Versus Reduced-Dose Betrixaban in the Acute Medically Ill VTE (Venous Thromboembolism) Prevention With Extended-Duration Betrixaban (APEX) trial.	In cohort 1 (D-dimer $\geq 2 \times$ ULN), VTE was significantly reduced among subjects treated with 80 mg of extended-duration betrixaban vs enoxaparin (6.27% vs 8.39%, RR = 0.74 [0.58-0.96], $P = 0.023$ ), and similarly in the entire primary efficacy outcome population (4.87% vs 7.06%, RR = 0.70 [0.56-0.87], $P = 0.001$ ). The study suggests that the efficacy of betrixaban is mainly driven by the full-dose stratum. The dosage of 40 mg daily may be overadjusted.	<i>Am Heart J.</i> 2017 Mar;185:93-100.	10.1016/j.ahj.2016.12.004

Table 4 (Continued)

Topic	Title	Most Important Takeaway Finding	Reference	DOI
Fatal and Irreversible Events	Comparison of Fatal or Irreversible Events With Extended-Duration Betrixaban Versus Standard Dose Enoxaparin in Acutely Ill Medical Patients: An APEX Trial Substudy.	Fatal or irreversible event is a composite of safety (fatal bleeding or ICH) and efficacy (CV death, MI, PE, or ischemic stroke) outcomes with permanent tissue damage or clinical harm. In cohort 1, fatal or irreversible events were reduced by betrixaban vs enoxaparin at 42 days (3.54% vs 4.80%; HR = 0.73; $P = 0.033$ ) and 77 days (4.36% vs 6.27%; HR = 0.70; $P = 0.005$ ). In all patients, betrixaban reduced fatal or irreversible events at 42 days (2.90% vs 4.08%; HR = 0.71; $P = 0.006$ ) and 77 days (3.64% vs 5.17%; HR = 0.70; $P = 0.002$ ).	<i>J Am Heart Assoc.</i> 2017 Jul 11;6(7). pii: e006015.	10.1161/JAHA.117.006015
Patient X	When Academic Research Organizations and Clinical Research Organizations Disagree: Processes to Minimize Discrepancies Prior to Unblinding Of Randomized Trials.	There was a discrepancy in APEX primary results between CRO and ARO, in which ARO analysis showed significant VTE reduction in cohort 1 (6.9% vs 8.5%; RR = 0.802 [0.644-0.998]; $P = 0.048$ ). The paper also provides guidance on how to minimize such discrepancy.	<i>Am Heart J.</i> 2017 Jul; 189:1-8.	10.1016/j.ahj.2017.03.018
Competing Risk	Competing Risk Analysis in a Large Cardiovascular Clinical Trial: An APEX substudy.	After accounting for competing risk of non-VTE-related death, betrixaban remained associated with a lower VTE risk compared with enoxaparin (SHR = 0.65 [0.42–0.99]; $P = 0.046$ ). The results reinforce the efficacy of betrixaban in VTE prophylaxis.	<i>Pharm Stat.</i> 2017 Nov; 16(6):445-450.	10.1002/pst.1823
IMPROVEDD Score	The IMPROVEDD VTE Risk Score: Incorporation of D-Dimer into the IMPROVE Score to Improve Venous Thromboembolism Risk Stratification.	D-dimer was independently associated with symptomatic VTE at 77 days (HR = 2.22 [1.38–5.38]; $P = 0.0010$ ). Incorporating D-dimer into the IMPROVE score refined its performance in discrimination and reclassification. Patients with IMPROVEDD score $\geq 2$ had a greater risk of symptomatic VTE than those with score of 0-1 (HR = 2.73 [1.52-4.90]; $P = 0.0007$ ), supporting its usefulness in identifying high-risk patients. The weight for D-dimer in the IMPROVEDD score matches the enrollment criteria of MARINER trial, in which patients with IMPROVE $\geq 4$ or 2-3 plus positive D-dimer were enrolled.	<i>TH Open.</i> 2017 Jun;1(01): e56-65.	10.1055/s-0037-1603929

Table 4 (Continued)

Topic	Title	Most Important Takeaway Finding	Reference	DOI
Bivariate Analysis	Effect of Axtended-duration Thromboprophylaxis on Venous Thromboembolism and Major Bleeding Among Acutely Ill Hospitalized Medical Patients: A Bivariate Analysis.	In the bivariate analysis that assumes a nonlinear relationship between symptomatic VTE and major bleeding, full-dose betrixaban was favorable over enoxaparin with respect to benefit-risk trade-off. Other regimens (extended enoxaparin, apixaban, and rivaroxaban) did not show a favorable net benefit over shorter-duration enoxaparin.	<i>J Thromb Haemost.</i> 2017 Oct;15(10):1913-1922.	10.1111/jth.13783
NT-proBNP	N-Terminal Pro-B-Type Natriuretic Peptide and the Risk of Stroke Among Patients Hospitalized with Acute Heart Failure: An APEX Trial Substudy.	NT-proBNP ( $\geq 1975$ ng/L) was independently associated with an increased risk of stroke at 77 days (HR = 3.64 [1.35-9.83]; $P = 0.011$ ) after adjusting for thromboprophylaxis, CHA <sub>2</sub> DS <sub>2</sub> -VASc components, CrCl, D-dimer, CRP, and other stroke risk factors. Elevated NT-proBNP may be considered as an enrichment strategy in future adaptive trials of stroke prevention.	<i>J Thromb Thrombolysis.</i> 2017 Nov;44(4):457-465.	10.1007/s11239-017-1552-7
Rehospitalization	Extended-Duration Betrixaban Reduces the Risk of Rehospitalization Associated With Venous Thromboembolism Among Acutely Ill Hospitalized Medical Patients: Findings From the APEX Trial (Acute Medically Ill Venous Thromboembolism Prevention With Extended Duration Betrixaban Trial).	Betrixaban reduced the risk of VTE-related rehospitalization at 42 days (0.25% vs 0.75%) and at 77 days (0.45% vs 1.04%; HR = 0.44 [0.25-0.80]; $P = 0.0055$ ) in the overall population. Full-dose betrixaban also reduced rehospitalization at 42 days (0.24% vs 0.93%) and at 77 days (0.46% vs 1.25%; HR = 0.37 [0.20-0.70]; $P = 0.0015$ ). Rehospitalization is a clinically relevant endpoint in considering the totality of efficacy of hospital-associated VTE prophylaxis as it adversely impacts the patient outcome and economic burden.	<i>Circulation.</i> 2018 Jan 2;137(1):91-94.	10.1161/CIRCULATIONAHA.117.031187
Thrombus Burden	Thrombus Burden of Deep Vein Thrombosis and Its Association with Thromboprophylaxis and D-Dimer Measurement: Insights from the APEX Trial.	Compared with enoxaparin, betrixaban not only reduced the DVT risk at 42 days (RR = 0.76 [0.61-0.94]; $P = 0.013$ ) but also DVT thrombus burden ( $P = 0.012$ ). Baseline elevated D-dimer was associated with a 2-fold increased risk of DVT ( $P < 0.001$ ) as well as a greater thrombus burden ( $P < 0.0001$ ). The study proposed using compression ultrasound to quantify the DVT thrombus burden (ie, the number of involved venous beds). These findings also help explain the legacy phenomenon of extended anticoagulation.	<i>Thromb Haemost.</i> 2017 Dec;117(12):2389-2395.	10.1160/TH17-08-0538

Table 4 (Continued)

Topic	Title	Most Important Takeaway Finding	Reference	DOI
D-dimer and Efficacy	Association of D-dimer Levels with Clinical Event Rates and the Efficacy of Betrixaban versus Enoxaparin in the APEX Trial	For every 0.25 $\mu\text{g/mL}$ increase in D-dimer concentration, there was a 2% increase in the RR of VTE in both the betrixaban ( $P < 0.001$ ) and enoxaparin ( $P < 0.001$ ) treatment arms. Among patients with positive D-dimer, betrixaban was associated with a lower VTE at 42 days (5.4% vs 7.6%; OR = 0.69 [0.55-0.88]; $P = 0.003$ ) when compared with enoxaparin. Note: This study used central D-dimer measurements (local values were imputed if central values were missing).	<i>TH Open.</i> 2018 Jan;2(01):e16-24.	10.1055/s-0037-1615288
Symptomatic VTE	Symptomatic Event Reduction With Extended-Duration Betrixaban in Acute Medically Ill Hospitalized Patients	The study assessed the efficacy of betrixaban in reducing symptomatic events (symptomatic proximal or distal DVT, nonfatal PE, or VTE-related death). Betrixaban reduced symptomatic VTE at 42 days (HR = 0.65 [0.42-0.99]; $P = 0.044$ ) and at 77 days (HR = 0.55 [0.37-0.83]; $P = 0.003$ ). Nonfatal pulmonary embolism was also significantly reduced at 77 days (HR = 0.45 [0.21-0.99]; $P = 0.041$ ).	<i>Am Heart J.</i> 2018 Apr;198:84-90.	10.1016/j.ahj.2017.12.015
Betrixaban in Patients with Prior VTE	Increased Benefit of Betrixaban Among Patients With a History of Venous Thromboembolism: A Post-Hoc Analysis of The APEX Trial	About 8% of patients had a prior VTE, which was associated with a 4-fold increased risk of VTE (OR = 4.03 [3.06–5.30]; $P < 0.001$ ). Among these subjects, betrixaban reduced VTE (10.4% vs. 18.9%; RR = 0.57 [0.38-0.86]; $P = 0.006$ ; NNT = 12).	<i>J Thromb Thrombolysis.</i> 2018 Jan;45(1):1-8.	10.1007/s11239-017-1583-0
Anemia	Association of Anemia With Venous Thromboembolism in Acutely Ill Hospitalized Patients: An APEX Trial Substudy	Anemia at baseline was associated with a greater risk of symptomatic VTE (RR = 1.94 [1.27-2.98]; $P = 0.002$ ), symptomatic DVT (RR = 2.29 [1.12-4.68]; $P = 0.019$ ), and nonfatal PE (RR = 2.63 [1.22-5.65]; $P = 0.010$ ). After adjusting for thromboprophylaxis, D-dimer and other VTE risk factors, anemia remained associated with an increased likelihood of VTE (OR = 1.71 [1.09-2.69]; $P = 0.020$ ). Low hemoglobin also improved risk discrimination and reclassification after inclusion in the IMPROVE score.	<i>Am J Med.</i> 2018 Aug;131(8):972.e1-972.e7.	10.1016/j.amjmed.2018.03.031
Hypoalbuminemia	Inverse Relationship of Serum Albumin to the Risk of Venous Thromboembolism Among Acutely Ill Hospitalized Patients: Analysis from the APEX Trial	Among hospital inpatients anticoagulated with betrixaban or enoxaparin, there was a stepwise increase in VTE risk with low levels of albumin ( $P < 0.0001$ ). Low albumin (<35 g/L) was associated with a 2-fold greater odds for VTE compared with the top quartile ( $\geq 42$ g/L) (OR = 2.12 [1.59-2.82]; adjusted OR = 2.08 [1.49-2.91]). Addition of albumin measurement improved the performance of IMPROVE and Padua scores.	<i>Am J Hematol.</i> 2019 Jan;94(1):21-28	10.1002/ajh.25296

Table 4 (Continued)

Topic	Title	Most Important Takeaway Finding	Reference	DOI
Asymptomatic DVT and Mortality	Asymptomatic Deep Vein Thrombosis is Associated with an Increased Risk of Death: Insights from the APEX Trial	<p>Among medical inpatients, development of an asymptomatic proximal DVT at 32-47 days was associated with a 3-fold increase in the subsequent mortality risk at 77 days (HR = 2.87 [1.48-5.57], <math>P = 0.001</math>) despite anticoagulation.</p> <p>A positive trend was observed between greater DVT thrombus burden and mortality (<math>P = 0.019</math>).</p> <p>These findings support the prognostic importance of an asymptomatic DVT endpoint.</p>	<i>Thromb Haemost.</i> 2018 Dec;118(12):2046-2052	10.1055/s-0038-1675606
Critically ill Patients	Extended-Duration Betrixaban Versus Shorter-Duration Enoxaparin for Venous Thromboembolism Prophylaxis in Critically Ill Medical Patients: An APEX Trial Substudy	<p>Compared with shorter-duration enoxaparin, critically ill medical patients who received extended-duration betrixaban had fewer VTE (4.27% vs 7.95%, <math>P = 0.042</math>) without more major bleeding events (1.14% vs 3.13%, <math>P = 0.07</math>).</p> <p>Both VTE (3.32% vs 8.33%, <math>P = 0.013</math>) and major bleeding (0.00% vs 3.26%, <math>P = 0.003</math>) were decreased in the full-dose stratum (ie, patients who had no severe renal insufficiency or P-glycoprotein inhibitor use).</p> <p>In this population, the benefit of prophylaxis with betrixaban was driven by preventing asymptomatic thrombosis and offset by an elevated risk of nonmajor bleeding.</p>	<i>Intensive Care Med.</i> 2019 Apr;45(4):477-487	10.1007/s00134-019-05565-6
Major Cardiac Adverse Event	Reduction of Cardiovascular Mortality and Ischemic Events in Acute Medically Ill Patients: An APEX Substudy	<p>At 42 days, betrixaban was associated with a reduction in MACE (CV death, MI, or stroke) compared with enoxaparin (2.4% vs 3.5%; HR, 0.69; 95% CI, 0.52-0.90; <math>P = 0.006</math>; ARR, 1.1%; NNT, 91).</p> <p>At 77 days, the reduction by betrixaban remained unchanged (2.9% vs 4.3%; HR, 0.68; 95% CI, 0.53-0.87; <math>P = 0.002</math>; ARR, 1.4%; NNT, 72).</p> <p>CV death was lower in the betrixaban group than enoxaparin group at 42 days (2.0% vs 2.7%; HR, 0.72; 95% CI, 0.53-0.98; <math>P = 0.034</math>; ARR, 0.7%; NNT, 143) and 77 days (2.4% vs 3.3%; HR, 0.75; 95% CI, 0.57-0.98; <math>P = 0.038</math>; ARR, 0.9%; NNT, 112).</p>	<i>Circulation.</i> 2019 Feb 26;139(9):1234-1236	10.1161/CIRCULATIONAHA.118.038654

Table 4 (Continued)

Topic	Title	Most Important Takeaway Finding	Reference	DOI
Major and Nonmajor Bleeding Events	Characterization of Major and Clinically Relevant Non-Major Bleeds in the APEX Trial	A total of 25 (0.7%) and 21 (0.6%) major bleeds occurred in the betrixaban and enoxaparin arms, respectively ( $P = NS$ ) A total of 91 (2.5%) and 38 (1.0%) clinically relevant nonmajor bleeds occurred in the betrixaban and enoxaparin arm ( $P < 0.001$ ), respectively. Rates of major or nonmajor bleeds resulting in new or prolonged hospitalization (44.0 vs 28.6%; 12.1 vs 21.1%) or study treatment interruption or cessation (72.0 vs 71.4%; 71.3 vs 68.4%) were similar between treatment arms.	<i>TH Open.</i> 2019 Apr 17;3(2): e103-e108.	10.1055/s-0039-1685496
Duration of Treatment	Extended-Duration Betrixaban Versus Shorter-Duration Enoxaparin for Venous Thromboembolism Prophylaxis in Critically Ill Medical Patients: An APEX Trial Substudy	At 35-42 days, extended betrixaban reduced the risk of VTE (4.27% vs 7.95%, $P = 0.042$ ) without causing excess major bleeding (1.14% vs 3.13%, $P = 0.07$ ). Patients who received betrixaban had more nonmajor bleeding than enoxaparin (population: 2.56% vs 0.28%, $P = 0.011$ ; full-dose: 3.32% vs 0.36%, $P = 0.010$ ). Mortality was similar at the end of study (population: 13.39% vs 16.19%, $P = 0.30$ ; full-dose: 13.65% vs 16.30%, $P = 0.39$ ).	<i>Intensive Care Med.</i> 2019 Apr;45(4):477-487.	10.1007/s00134-019-05565-6
Serum Albumin	Inverse Relationship of Serum Albumin to the Risk Of Venous Thromboembolism Among Acutely Ill Hospitalized Patients: Analysis from the APEX Trial	Patients at the bottom albumin quartile ( $<35$ g/L) had a 2-fold greater odds for developing VTE compared with the top quartile ( $\geq 42$ g/L) (OR = 2.119 [95% CI, 1.592-2.820]; adjusted OR = 2.079 [1.485-2.911]). Patients with albumin $<35$ g/L had a greater risk of VTE (OR = 1.623 [1.260-2.090]; adjusted OR = 1.658 [1.209-2.272]) when compared with patients with albumin $\geq 35$ g/L in a propensity score-matched pairs approach.	<i>Am J Hematol.</i> 2019 Jan;94 (1):21-28.	10.1002/ajh.25296

ARO = academic research organization; ARR = absolute relative risk; CHA<sub>2</sub>DS<sub>2</sub>-VASC = Congestive heart failure, Hypertension, Age 75 years or older, Diabetes mellitus, Stroke, transient ischemic attack, or thromboembolism, Vascular disease, Age 65-74, Sex category (female); CI = confidence interval; CrCl = creatinine clearance; CRO = clinical research organization; CRP = C-reactive protein; CV = cardiovascular; DVT = deep vein thrombosis; HR = hazard ratio; ICH = intracerebral hemorrhage; MI = myocardial infarction; NNT = number needed to treat; OR = odds ratio; PE = pulmonary embolism; RR = relative risk; SHR = sub distribution hazard; VTE = venous thromboembolism.



events, with no difference in mortality. The guidelines, therefore, identify post-discharge prophylaxis as a priority for future research.<sup>60</sup> Of note, the recommendations do not comment on the risk stratification of patients in the APEX trial, nor do they include data from the MARINER trial, which was published after the guidelines were released.

Appropriately identifying patients at a high risk for VTE is the key to determining which patients will benefit from extended-duration post-hospital VTE prophylaxis. Subpopulations of medically ill patients may derive benefit, but individual patient risks and benefits should be assessed.

## POPULATION MANAGEMENT AND THE ROLE OF HOSPITAL MEDICINE

### Post-Discharge Venous Thromboembolism Prophylaxis

Approximately 75% of patients with hospital-associated VTE in the United States are diagnosed after discharge.<sup>4</sup> This estimate is based on a sampling of patients from Olmstead County in Rochester, Minnesota. In Mayo Clinic hospitals, VTE prophylaxis rates increased dramatically, yet there was no appreciable decrease in the rate of VTE. Similarly, top-performing hospitals—institutions with a mean pharmacologic prophylaxis rate of 85.8% on admission—had no appreciable 90-day post-admission hospital-associated symptomatic VTE rates compared with low-performance (55.5% mean prophylaxis) institutions (1.27 vs 1.15 per 10,000 patient-days, respectively).<sup>13</sup>

### Preventable Events During Hospitalization and After Discharge in the Era of Prospective Payment

The Inpatient Prospective Payment System (IPPS), managed by the Centers for Medicare & Medicaid Services (CMS), compensates health care organizations for providing inpatient care to Medicare subscribers. The Hospital Readmissions Reduction Program (HRRP) is a key initiative within the IPPS that has financial consequences for health care organizations. HRRP quantifies readmission ratios for every health care institution based on the expected readmission rates for several diagnoses: acute myocardial infarction, heart failure, pneumonia, chronic obstructive pulmonary disease, coronary artery bypass graft surgeries, and elective primary total hip arthroplasty or total knee arthroplasty. Higher ratios result in payment reductions of up to 3%. Improvements in VTE-associated metrics can positively impact the payments received by health care organizations. Studies estimate that 45%-57% of medical patients who develop VTE as a complication of admission sustain the event after hospital discharge.<sup>1,32,61</sup> Therefore, increased use of VTE prophylaxis could result in fewer VTE-related readmissions and improved readmission metrics.

CMS requires health care organizations to submit several other metrics as well, including electronic clinical quality

measures (eCQMs) and measures for the Hospital Compare (HC) website.<sup>62</sup> Pertinent eCQM metrics include Joint Commission VTE-1 and VTE-2, which quantify the number of patients who receive VTE prophylaxis on admission to the general hospital and to the ICU, respectively. A health care organization can choose which measures they wish to submit from the eCQM list, though eCQMs are not publicly reported. The HC website reports on a wide array of metrics that factor into an overall hospital rating, one of which is the VTE-6 metric. This metric—Hospital-Acquired Potentially Preventable VTE—captures the number of nosocomial VTE events that occur in patients who did not receive prophylaxis prior to developing VTE. Unlike eCQMs, the information on the HC website is publicly available.

Of note, eCQM and HC website measures are not currently used to levy financial penalties against institutions. Nevertheless, targeting preventable VTE during and after hospitalization can improve a health care organization's performance in these programs.

## PATTERNS OF CARE DELIVERY AND TRANSITION MODELS

### Rounding and Discharge Recommendations

In acute medically ill patients, the risk of VTE and bleeding should be periodically assessed during hospital admission, and prophylactic strategies should be adjusted accordingly. Prophylaxis should continue until the patient is fully ambulatory or until hospital discharge. However, evidence for prophylaxis is less well-documented in patients who are not ambulatory and are residing in long-term facilities. There is a paucity of evidence in nursing home populations.<sup>63-65</sup> Nursing home residents theoretically have an increased risk for VTE because of post-acute medical illness, immobility, cancer, age, and postsurgical status.<sup>66</sup> Nevertheless, some data have shown that traditional VTE risk factors in non-nursing home populations do not apply to the nursing home population. One study identified respiratory infection, substantial mobility limitations, and recent general surgery as the only independent risk factors for VTE and concluded that prophylaxis should be considered in nursing home patients with these issues.<sup>67</sup> The role of thromboprophylaxis in the nursing home setting remains controversial and requires further research.<sup>68</sup>

### Communication and Transition-of-Care Recommendations

Communication is crucial to ensure that appropriate prophylaxis recommendations are addressed during transitions of care. Before discharging a patient at risk for VTE, a health care professional should consider educating patients at high risk for VTE about the signs and symptoms of VTE.<sup>69,64</sup> If prophylactic medications are prescribed, patients should be aware of the indication, proper usage, duration, and side effects. Communication about discharge prophylaxis should routinely occur among the primary care provider, hospital provider, and patient to establish care

coordination and continuity of care.<sup>70,71</sup> Studies indicate that primary care providers “very much prefer” to communicate with hospitalists by telephone during admission and discharge.<sup>72,73</sup> This means that primary care providers may need to create an office strategy in which hospitalists can reach them with minimal delay. Optimizing communication pathways is critical because primary care providers resume care of their patients after discharge.

## Resources and Solutions to Ensure Adherence

Although recent evidence corroborates the efficacy and safety of extended prevention strategies for VTE, a review of current literature identifies several system-level, provider-level, and patient-related barriers that hinder adherence to VTE guidelines. System-level barriers include time limitations, cost, resource utilization, and a lack of available reminder systems and counseling materials.<sup>74,75</sup> Provider-related barriers include a lack of awareness of VTE risk, complex practice recommendations, concerns about bleeding, and failure to use evidence-based guidelines.<sup>74</sup> Patient-related factors include refusal of VTE prophylaxis<sup>76-79</sup> and a general lack of knowledge about VTE.<sup>80</sup>

Aggregate data from prior studies suggest that a multidisciplinary team approach, continuous collaboration with stakeholders at all levels (ie, institutional leaders, experts, physicians, nurses, pharmacists, and patients), and combined patient- and provider-facing strategies are the most effective ways to implement successful practices.

System-level barriers are best addressed with the use of computerized tools and order sets, alert systems, or active reminders. The passive dissemination of guidelines is found to be least effective.<sup>81</sup> The VTE Computerized Clinical Decision Support (CDS) tool, embedded in specialty-specific admission and transfer order sets, has helped providers assess patients’ VTE and bleeding risk factors. It offers standardized, evidence-based VTE prophylaxis order sets. When combined with a mandatory clinical workflow or a hard-stop interruption, VTE CDS ensured better adherence, reduced VTE incidence, and improved consistency of care.<sup>82-84</sup>

Active reminders and best-practice alert systems encompass computer alerts<sup>47,85</sup> or human alerts from staff members or pharmacists.<sup>86,87</sup> In 1 study, physicians who received a direct notification when they did not prescribe appropriate VTE prophylaxis were more likely to follow the recommendations. However, frequent e-alerts were sometimes ignored by ordering physicians.<sup>88</sup> This effect may be attributed to “alert fatigue” and warrants further investigation.

Educational interventions, audits, and performance feedback can also be used to address provider-level barriers. Providing personal feedback to a physician with scorecards and peer-to-peer coaching has improved adherence to recommendations.<sup>89</sup> Providing direct feedback via a real-time dashboard with financial incentives has also increased use of VTE prophylaxis.<sup>90</sup> Among nurses, routine assessment of VTE prophylaxis administration, feedback on omitted doses, and the use of educational modules decreased the number of missed

**Table 5** Resources and Solutions to Ensure Adherence of Venous Thromboembolism Prophylaxis During Stay Post-Discharge

Barriers	Strategies/Interventions
System level	<ul style="list-style-type: none"> <li>• Standardized protocol for:               <ul style="list-style-type: none"> <li>◦ Admission</li> <li>◦ Transfer</li> <li>◦ Perioperative care</li> </ul> </li> <li>• Discharge (on selected patients)</li> <li>• Mandatory order set with hard-stop interruption</li> <li>• VTE risk assessment tool</li> <li>• Bleeding risk tool</li> <li>• Alert system/active surveillance</li> </ul>
Provider level	<p>Physician</p> <ul style="list-style-type: none"> <li>• Electronic reminders, missed dose alert</li> <li>• Scorecard use</li> <li>• Individualized feedback</li> <li>• Financial incentive</li> <li>• Individualized dashboard</li> <li>• Education</li> <li>• Audit</li> </ul> <p>Nurse</p> <ul style="list-style-type: none"> <li>• Feedback on omitted dose</li> <li>• Education, web-based modules</li> </ul> <p>Pharmacist</p> <ul style="list-style-type: none"> <li>• Medication reconciliation</li> <li>• Medication adherence</li> </ul>
Patient and family level	<ul style="list-style-type: none"> <li>• Standardized nursing response to refusal</li> <li>• Patient and family education</li> </ul>

and refused doses.<sup>26,91</sup> Provider education is often a required component of a successful intervention but is effective only when combined with other strategies.<sup>92,93</sup>

Patient and family barriers are best addressed through education and engagement. One successful multidisciplinary, unit-based program included education, feedback, and a standardized nursing response to patient refusal of prophylaxis. The intervention was associated with an immediate and sustained decrease in missed and refused doses.<sup>26</sup> In another study, a 3-phase survey was conducted to inform a patient-centered approach to VTE education.<sup>94</sup> Based on these survey data, several educational materials were created for patients and caregivers, including paper brochures and a video (Table 5). The study also found that enhanced patient-provider communication successfully encouraged patients to take a more active role in learning about VTE. Finally, a study of pharmacist-led, individualized patient education sessions demonstrated improved adherence to VTE prophylaxis,<sup>80</sup> but the approach was labor-intensive, restricting generalizability.

## ORDER SET AND ELECTRONIC DECISION SUPPORT FOR VENOUS THROMBOEMBOLISM PREVENTION IN HOSPITALIZED MEDICALLY ILL PATIENTS

Electronic health record (EHR)-based quality improvement strategies, specifically alert-based CDS tools, have improved thromboprophylaxis utilization among medical

patients who are hospitalized and have great potential for optimizing VTE prevention after discharge.<sup>95</sup> In a single-center, randomized controlled trial of 2506 patients, an alert-based CDS strategy was used to promote thromboprophylaxis and reduce rates of symptomatic DVT and PE.<sup>47</sup> A computer program linked to the EHR and provider order entry system used a validated risk score to identify hospitalized patients at high risk for VTE who did not receive prophylaxis. The software randomly assigned these patients to an intervention arm, where a VTE risk alert was flagged for the provider ( $n = 1255$ ), or to a control arm ( $n = 1251$ ), where no provider alert notification was triggered. Clinicians who received the alert had to acknowledge the notification and could then withhold or initiate pharmacologic or mechanical prophylaxis. The alert system was linked to the hospital's online VTE guidebook, which included clinical guidelines around prophylactic regimens. The primary endpoint was the rate of clinically diagnosed symptomatic VTE within 90 days of follow-up.

The alert-based CDS strategy increased the rate of thromboprophylaxis (33.5% vs 14.5%,  $P < 0.0001$ ) compared with the control group. The alert-based CDS strategy group had higher rates of both pharmacological (23.6% vs 13.0%,  $P < 0.001$ ) and mechanical (10.0% vs 1.5%,  $P < 0.001$ ) prophylaxis compared with control patients. The CDS intervention also reduced the risk of symptomatic VTE by 41% (HR 0.59; 95% CI, 0.43-0.81;  $P = 0.001$ ); however, there was a notable difference in VTE rates between the intervention and control arms regardless of prophylaxis use that could not be readily explained. In addition, there was no significant difference in mortality or in rates of major or minor bleeding between the 2 groups.

In another study of an alert-based CDS strategy, providers were instructed to enter a rationale if they declined to order prophylaxis after an initial alert. The CDS then provided a final opportunity to prescribe graduated compression stockings or intermittent pneumatic compression devices. Within the CDS, physicians generated thromboprophylaxis orders for an additional 58.4% of their high-risk patients after initially declining to move forward with prophylaxis.<sup>96</sup>

Because many hospitals do not have the necessary infrastructure and resources to implement alert-based CDS, studies have also evaluated "human" rather than electronic notification strategies. Although no head-to-head comparisons have been performed between the 2 decision support modalities, an alert-based CDS strategy appears to be more effective for the prevention of VTE among patients who are hospitalized. A randomized controlled trial of 2493 patients assessed the impact of a noncomputerized physician alerting strategy and found that "human alerts" were effective for increasing thromboprophylaxis utilization in patients who were hospitalized (46.0% vs 20.6%,  $P < 0.0001$ ) but were not as useful for reducing symptomatic VTE.<sup>86</sup> In another trial of a nonelectronic decision support strategy, prescription of extended-duration, post-discharge thromboprophylaxis increased, but there was no impact on symptomatic VTE.<sup>97</sup>

A CDS approach may be favorable for several reasons. First, an alert-based CDS system may be more difficult to ignore because the alert occurs at the point of care and forces the provider to acknowledge the notification before proceeding.<sup>98</sup> Second, unlike approaches using a human alert, CDS programs can integrate a wide range of clinical tools, including evidence-based guidelines and risk-scoring systems.<sup>95</sup> Finally, CDS tools designed to improve thromboprophylaxis may better maintain effectiveness over time than strategies using human alerts.<sup>99</sup>

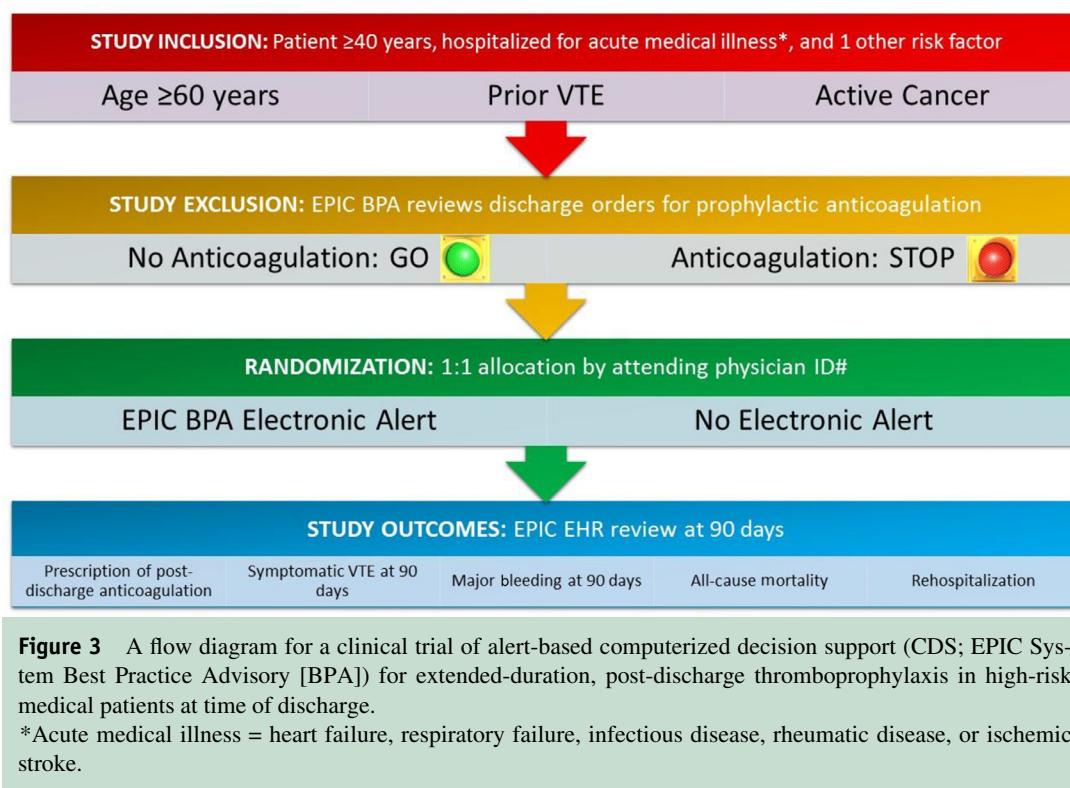
Alert-based CDS systems have particular value in provider education within the context of clinical care, especially when knowledge gaps are present. Given that the clinical benefit of extended-duration thromboprophylaxis in high-risk hospitalized medical patients has been questioned,<sup>5,6,53</sup> clinicians may not recognize indications for VTE prevention during transitions of care. A CDS program can assess VTE risk based on study inclusion criteria or validated risk scores. For patients with a high risk for VTE but no active order for thromboprophylaxis, an on-screen CDS alert can notify the provider about the increased post-discharge risk and outline indications for thromboprophylaxis after hospitalization. The CDS tool can then be linked to an on-screen order template that gives the provider options for extended-duration thromboprophylaxis. A randomized controlled trial can be envisioned to evaluate the impact of the alert-based CDS strategy on both the prescription of thromboprophylaxis and the frequency of symptomatic VTE (Figure 3). A trial is currently underway to assess whether an alert-based CDS is effective in closing knowledge gaps around VTE prevention in medical patients who are hospitalized and at high risk (NCT03728166). Additional research on CDS strategies for VTE prevention is warranted given the rapid advances in the field.<sup>100</sup>

## QUALITY AND SAFETY: HOSPITAL VENOUS THROMBOEMBOLISM SCORECARDS AND SAFETY DASHBOARDS

Because a large number of VTE events are directly related to patient hospitalization,<sup>101</sup> hospitals have an obligation to provide risk-appropriate VTE prophylaxis. Nevertheless, fewer than 50% of hospitals successfully administer appropriate, evidence-based VTE prophylaxis.<sup>102</sup> A multi-pronged approach is needed to optimize VTE risk reduction and mitigate patient harm. Hospital leadership can further encourage effective VTE prophylaxis by implementing 2 quality improvement tools proven to bolster patient safety: dashboards and scorecards.

### Dashboards

A dashboard is a concise and easily readable display of the key performance indicators that a hospital wishes to monitor in real time (or near real time). It provides a single view (usually graphical) of actionable data that is readily



accessible. A dashboard is typically used by hospital operational leads or frontline clinicians.

Dashboards have been successfully used in a variety of clinical care and in-hospital patient safety scenarios, including VTE prophylaxis. Having access to information at a granular level enables instant identification of patients receiving absent or inappropriate prophylaxis, which in turn allows for immediate intervention. This process of real-time measurement with subsequent intervention has been termed “measure-vention” and has demonstrated significant improvement of appropriate VTE prophylaxis in national collaborative efforts<sup>102</sup> (Figure 4).

In a retrospective analysis of 3144 inpatient admissions at a tertiary care hospital, rates of VTE prophylaxis among hospitalists were examined following implementation of an individualized physician dashboard.<sup>90</sup> After 6 months of physician feedback from a web-based dashboard, guideline-compliant VTE prophylaxis rates improved significantly. Interestingly, the dashboard demonstrated a faster rate of improvement than the subsequent study intervention, which was a pay-for-performance program.

### Scorecards

A scorecard is a high-level, brief report providing an overview of a hospital’s performance against its projections and improvement goals. It evaluates the success or failure of efforts in general terms (ie, “on target,” “at risk,” “below target”) and uses simple visualizations (ie, raw numbers, arrows, red/green/yellow colors). In addition to tracking

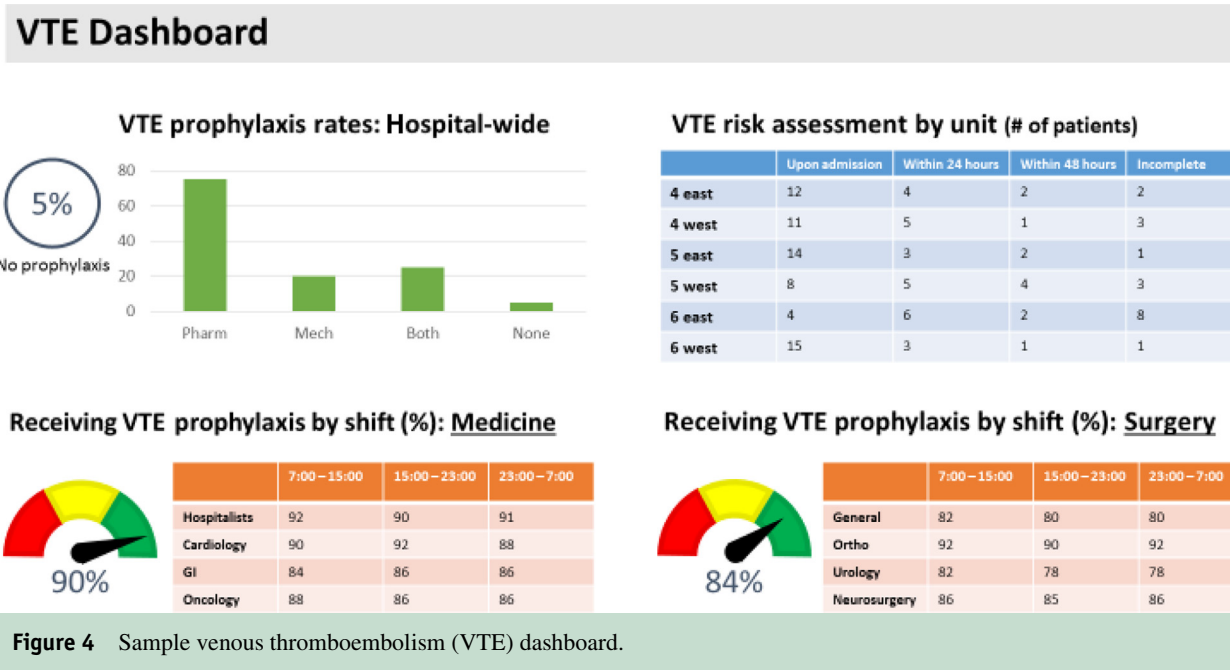
hospital performance at timely intervals, scorecards also allow comparison to national standards (Figure 5).

In a prospective study of 49 surgical residents at an academic medical center, individualized scorecards were used to provide timely feedback on the use of appropriate VTE prophylaxis.<sup>91</sup> After scorecard implementation, the prescription of appropriate prophylaxis increased.

### Real-World Applications of Dashboards and Scorecards

Recently, the Centers for Disease Control and Prevention (CDC) launched the Healthcare-Associated VTE Prevention Challenge to identify, highlight, and reward institutions that implemented innovative, effective, and sustainable strategies to prevent VTE events.<sup>103</sup> One of the popular strategies consisted of providing real-time feedback, scorecards, and dashboards for providers and organizations to monitor VTE prevention performance and identify areas for improvement.

Hospitals and health systems striving to optimize VTE prophylaxis efforts in patients who are hospitalized may have great success with the implementation of dashboards and scorecards. Dashboards should be succinct, easily readable, and capable of real-time (or near real-time) monitoring. Scorecards should be high level and able to provide a brief overview of hospital VTE prophylaxis performance. The development of such tools is relatively straightforward, but collaboration with hospital information technology staff is advised.



### THE ROLE OF THE PHARMACIST TO ENSURE EDUCATION AND IMPROVE ADHERENCE

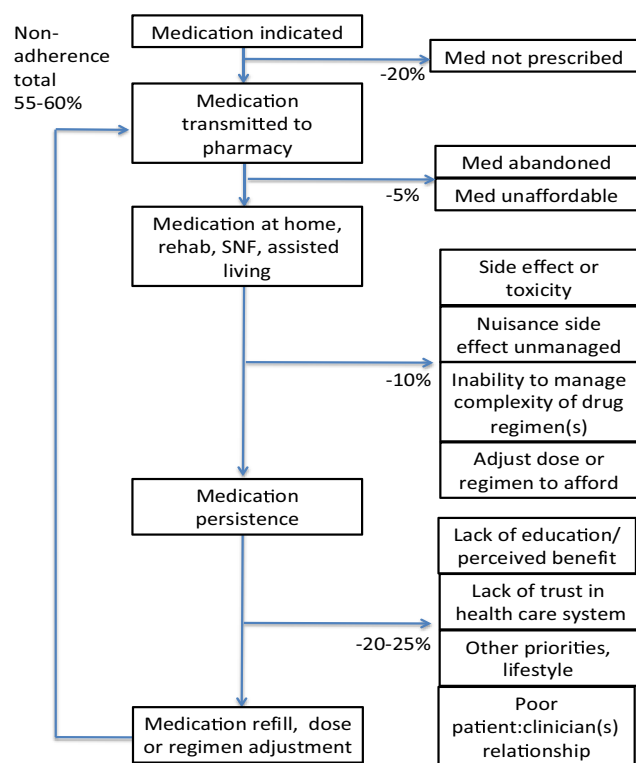
Obstacles arise when patients are directed to obtain medications and comply with a regimen, and challenges continue over the course of therapy (Figure 6).<sup>104-110</sup> Adherence to chronic anticoagulation therapy falls to approximately 50% after 1 year.<sup>111</sup> Even time-limited 14- to 35-day courses of prophylactic anticoagulants are associated with only 80% adherence.<sup>112</sup> Medication nonadherence is associated with an increased risk of major adverse cardiac events, hospitalization rates, and higher costs.<sup>113</sup> Pharmacists are a valuable resource to support sound medication behaviors and adherence. They can help to ensure medication access and provide education, monitoring, and support. These tasks are often included as part of a structured Anticoagulation Management Service.

Several studies have shown that pharmacist-based, patient-focused activities, typically including medication reconciliation, education, and follow-up surveillance, can improve outcomes. In 1 patient intervention, tailored education about medication dosing, storage, and side effects, along with adherence and adverse event monitoring, improved adherence from 65% to ≈80% over 3- and 12-month periods.<sup>114</sup> A similar multifaceted pharmacist intervention with medication reviews, patient interviews, and follow-up reduced patient readmissions and emergency department visits.<sup>115</sup>

An ongoing in-hospital intervention that includes medication reconciliation, patient education, and scripted follow-up phone calls is known as “Meds-to-Beds.” The program has been instituted at several US hospitals and delivers bedside medications to patients, ensures medication access, and removes financial barriers when present.

VTE Goals	Target	Owner	Review Frequency	May 2016	June 2016	July 2016	YTD 2016
Risk assessment	90%	Quality lead	Monthly	94%	96%	90%	94%
Appropriate prophylaxis given	90%	Physician lead	Monthly	86%	82%	91%	86%
In-hospital acquired VTE events	≤5	Safety lead	Monthly	4	8	5	5
30-day hospital acquired VTE events	≤20	Physician champion	Monthly	16	12	24	19
Potentially preventable VTE events	0	Physician champion	Monthly	1	0	2	1

**Figure 5** Sample hospital venous thromboembolism (VTE) scorecard.



**Figure 6** Obstacles to medication adherence. SNF = skilled nursing facility.

\*Percentages reflect the percentage of patients estimated to stop taking their medication.

One study showed that patients who participated in a bedside delivery program and received a follow-up call were readmitted less frequently (5%) compared with patients who received usual care (9.5%).<sup>116</sup>

In patients with low-income status and low health literacy, pharmacists have been employed to provide intensive counseling, adherence aids, and follow-up contact.<sup>117</sup> In a study using a multilevel medication management program, medication adherence was 79% in the intervention group compared with 68% in the usual care group. The intervention group also had reduced health care costs and 20% fewer emergency department visits and hospital admissions. However, another study using the same pharmacist-intervention tactics failed to reduce medication errors and adverse drug events compared with usual care.<sup>118</sup>

Although labor intensive, most pharmacist interventions appear to improve adherence. Technological interventions have not been as successful. One study evaluated the low-cost strategies of pillboxes, timer/alarm caps for medication vials, and bottle strip reminders for patients taking up to 3 medications.<sup>119</sup> There was no difference in adherence between the usual care group and patients using any of the devices. Another study employed a smartphone intervention that included reminder alerts, adherence reports, and optional peer support. After 12 weeks, there was only a slight improvement in medication adherence but no difference in clinical outcomes between the smartphone users

and the usual care group.<sup>120</sup> The FDA approved a medication combined with an ingestible sensor that can transmit medication-taking activities to a wearable patch and on to a provider.<sup>121</sup> Similarly, the impact of novel technologies on medication adherence, such as virtual personal assistants (eg, Apple-Siri, Microsoft-Cortana, Amazon-Alexa, etc.) and countertop medication-dispensing stations (eg, Pillo, MedSentry, Livi), is under investigation.

## RECOMMENDED ACTION STEPS

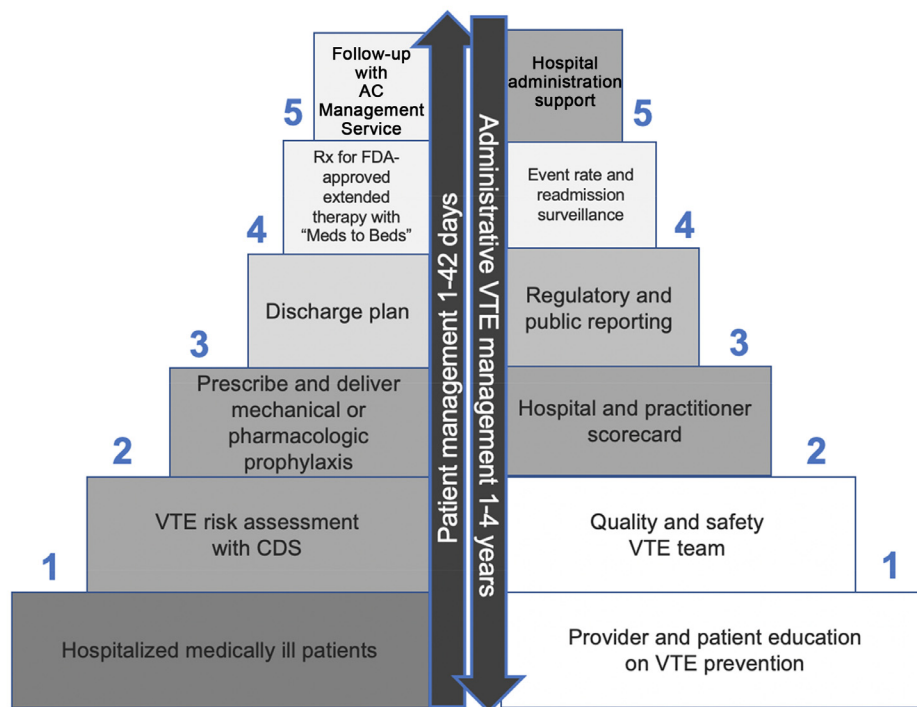
There remains a subset of acutely ill medical patients who are hospitalized and who will develop VTE after hospital discharge. Professional guidelines do not support routine prescribing of extended thromboprophylaxis, yet both betrixaban and rivaroxaban administration have reduced symptomatic VTE events in this vulnerable population. **Figure 7** demonstrates evidence-based recommendations regarding clinical practice principles for extended VTE prophylaxis.

The Anticoagulation Action Initiative endorses the following action steps:

1. We believe acutely ill medical patients should be assessed for VTE risk on admission with a validated RAM such as Padua, IMPROVE, Kucher, Intermountain, Caprini, or Geneva, with model selection based on institutional preference. The RAM should be incorporated into the EHR and optimized with alert-based CDS.
2. Thromboprophylaxis should be routinely offered to providers via prescribing order sets or treatment pathways.
3. Hospital departments that are responsible for reporting quality data to state and federal regulatory agencies (eg, the Department of Quality and Safety) should provide guidance about prescription and treatment pathways to frontline clinicians. Reporting processes should be bolstered with real-time dashboards and scorecards that outline required steps for thromboprophylaxis delivery and provide performance metrics.
4. Increasing clinician awareness about hospital-acquired and post-discharge VTE events is an essential first step in the development of successful future interventions. We support a multidisciplinary approach to VTE prevention.
5. At the time of hospital discharge, we recommend a discussion with the patient and family about VTE risk in the appropriate high-risk population.
6. When VTE remains a heightened concern, we recommend that providers thoughtfully consider extended thromboprophylaxis.
7. When thromboprophylaxis is deemed necessary, we advocate an evidence-based approach with an FDA-approved agent that is indicated for extended thromboprophylaxis.
8. To remove financial barriers and reinforce medication adherence, we support a “Meds-to-Beds” program with direct clinician-patient interaction and education.

# Venous Thromboembolism Prevention Action Steps

## Patient-Centered Care



**Figure 7** Necessary action steps required for extended venous thromboembolism (VTE) prophylaxis in acute medical illness. AC = anticoagulation; CDS = computerized decision support; VTE = venous thromboembolism.

9. When available, we recommend that patients requiring extended thromboprophylaxis be supported with clinician follow-up, either via pharmacist surveillance or enrollment in a structured Anticoagulation Management Service.

## CONCLUSION

Medically ill patients represent a vulnerable population with significant risk for VTE during and after hospitalization. The NATF Anticoagulation Action Initiative assesses the current landscape of in-hospital and post-discharge VTE prophylaxis, explores new data on the utility of direct oral anticoagulants for post-discharge prophylaxis, and provides comprehensive recommendations to aid frontline clinicians in caring for patients before and after discharge. Institution-wide initiatives to promote awareness around post-discharge VTE risk can further optimize care delivery in the era of clinical practice measures, value-based purchasing, and the patient-centered experience.

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