REPORT

Venous Thromboembolism in Acute Medically Ill Patients: Identifying Unmet Needs and Weighing the Value of Prophylaxis

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Venous thromboembolism (VTE) events, which manifest as deep vein thrombosis (DVT) and/or pulmonary embolism (PE), cause considerable mortality and morbidity.[1] As many as 900,000 Americans each year experience VTE events, and as many as 150,000 to 200,000 deaths may be directly or indirectly related to VTE events.[2-4] DVTs, which manifest as clots in the deep veins of the body, are the most common form of VTE event; approximately two-thirds of VTE events are characterized as DVTs.[5] The most serious complication that can result from DVTs are PEs, and they occur in approximately one-third of patients with DVTs.[2,5] PEs, which develop when a portion of the DVT breaks off and enters the pulmonary arteries, account for 5% to 10% of US inpatient deaths annually.[6]

Risk factors for VTE events can be genetic, acquired, or transiently acquired (**Table**).[5,7-9] Using risk assessment models, several prediction scores have been proposed and implemented in clinical practice to stratify VTE risks in hospitalized patients.[6] The risk factors adopt weighted variables, such as hospitalization for medical illness; advanced age; past history of VTE or cancer; and reduced mobility commonly are considered key predictors for VTE. Additionally, subacute illnesses, inherited or acquired coagulation disorders, surgery, trauma, infection, obesity, estrogen therapy, or erythropoiesis-stimulating agents may also put patients at risk of VTE.[6-8]

VTE Events in Acute Medically Ill Patients

Hospitalization is considered the single most important risk factor for developing VTE events.[2] As broadly illustrated in **Figure 1**, patients who are hospitalized for acute medical illnesses such as pneumonia, acute respiratory failure, stroke, or heart failure have more than a tenfold increased risk of developing VTE events.[10-13]

In fact, 60% to 70% of all VTE events are reported in acute medically ill hospitalized patients, whereas the remainder are found in surgical patients.[1] Over 8 million acute medically ill patients each year in the United States are at risk for experiencing VTE events.[11] The risk of developing VTE continues beyond hospitalization, especially for the first 30 days after discharge.[14] Real-world data suggest that 4.8 million to 5.2 million patients may have an extended VTE risk.[1,6,10,12,13]

KEY TAKEAWAYS

- Over 8 million acute medically ill patients each year in the United States are at risk for experiencing venous thromboembolism (VTE) events, with up to 900,000 patients developing blood clots for the first time.
- Patients who are hospitalized for acute medical illnesses (eg, pneumonia, stroke particularly ischemic stroke, and heart failure) have more than a 10-fold increased risk of developing VTE events compared to those who are not hospitalized.
- In acute medically ill patients, the risk of experiencing VTE events remains high after hospitalization, especially within the first 30 days post discharge.
- Up to 200,000 VTE-related events occur despite prophylaxis, with an estimated 40,000 deaths directly or indirectly related to VTE.
- In total, VTE events cost the US healthcare system $7 billion to $10 billion each year for newly diagnosed, medically-treated incident cases.
- Inpatient VTE prophylaxis rates are low, ranging from 30% to 60%; postdischarge (extended) prophylaxis rates are even lower, below 10%, typically because no approved extended regimens were available until recently.
- To date, several clinical trials have evaluated the use of extended-duration VTE prophylaxis with enoxaparin, apixaban, rivaroxaban, and betrixaban compared with standard-duration VTE prophylaxis with enoxaparin. At the current time, betrixaban is the only anticoagulant that has demonstrated clinical benefit and has been FDA-approved for postdischarge extended VTE prophylaxis in acute medically ill patients.
- An unmet medical need exists for improving the quality of VTE prophylaxis during hospitalization and after discharge in acute medically ill patients, decreasing thromboembolic disease burden and improving long-term patient outcomes.

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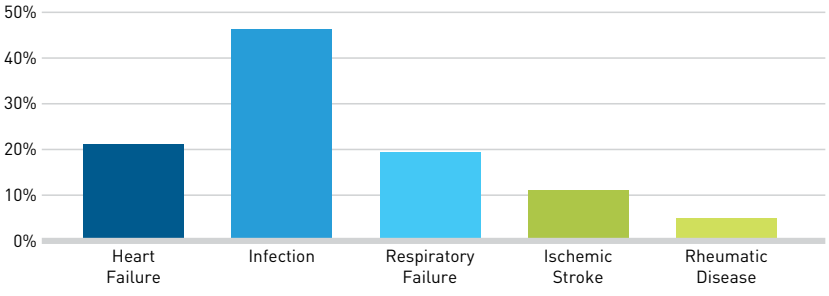
TABLE. Risk Factors Associated With Venous Thromboembolism Events[5,7-9]

Genetic	Acquired	Transiently Acquired
• Antithrombin deficiency • Factor V Leiden • Family history • Protein C deficiency • Protein S deficiency • Prothrombin G20210A • Sickle cell trait	• Advanced age (>40 years) • Antiphospholipid antibodies • Cancer • Chronic disease • Obesity • Smoking	• Blood transfusions • Erythropoiesis-stimulating agents • Hormone therapy (estrogen) • Hospitalization (medical or acute) • Immobilization • Indwelling central venous catherization • Infection • Long-distance travel • Oral contraceptives • Previous VTE event(s) • Pregnancy/postpartum • Surgery • Trauma

VTE indicates venous thromboembolism.
Table adapted from Beckman MG, Hooper WC, Critchley SE, Ortel TL. *Am J Prev Med*. 2010;38(suppl 4):S495-S501.

Stakeholders concurred that the occurrence of VTE events is a significant public health concern. According to Ralph J. Riello III, PharmD, "It is a problem often that hospitals do not know that they have or that exists." Moreover, George A. Davis, PharmD, observed, "we need to change the way we think about this problem by first thinking about it as a problem."

FIGURE 1. Percentage of Increased Risk for VTE in Patients Hospitalized for Acute Illnesses[10-13]



VTE indicates venous thromboembolism.

Clinical and Economic Burden of VTE Events

The risk of developing primary and/or recurrent VTE events remains high after hospitalization.[14] Serious complications, including death, can occur after VTE events. Joshua D. Lenchus, DO, BSPharm, observed that patients are at increased risk of recurrent thromboembolism and chronic morbidity (eg, venous insufficiency and pulmonary hypertension) following VTE events. Further, he noted that recurrence can also be high "following a standard course of anticoagulant therapy; approximately 33% of patients experience a recurrence within 10 years of the initial event, with the highest risk occurring during the first year." Regarding recurrent events, stakeholders discussed that the Centers for Medicaid and Medicare Services (CMS) sometimes penalize facilities when patients present with recurrent VTE events within the first 30 days of hospital discharge.

In the experience of Riello, typical recurrence is usually within 3 months of the first episode. He noted, "Many hospitals are not aware of their recurrent VTE rates." He suggested that 2 forms of education are needed: clinicians need to be educated about the risks, and patients need to be taught that the risk for VTE events does not stop once they leave the hospital. One study noted a 34% decrease in patient refusal (44% to 29%) when patients are educated adequately about the rationale for VTE prophylaxis.[15] Gary L. Johnson, MD, MS, MBA, encouraged providers/prescribers to openly discuss the need for thromboprophylaxis with patients and allow them to have "shared decision making" regarding treatment options.

An estimated 10% to 30% of patients suffer mortality within 30 days of experiencing a VTE event, with most deaths being related to PE events.[5] Some patients who initially survive a VTE event die within 90 days of hospital discharge.[16] Stakeholders noted that VTE events are the leading cause of preventable hospital deaths in the United States and agreed that prevention is paramount. In fact, up to 70% of hospital acquired VTE events are preventable (60% of healthcare associated VTE could have been prevented by universal VTE prophylaxis).[17]

VTE events are not only a major cause of morbidity and mortality in the US, but they also negatively affect quality of life (QOL).[5,18] "The QOL impact on these patients is significant," noted Lenchus. "We discharge them from the hospital, and then we give them drug X. There is a tremendous impact in terms of QOL," he said. According to the stakeholders, QOL can be impaired in physical, social, and psychological domains.

Compared with population norms in a general US population adjusted for age and sex, Van Korlaar et al found that patients experiencing VTE events scored significantly lower ($P < .05$) on all subscales of the Short-Form-36 (SF-36), a disease-specific venous thrombosis-quality of life (VT-QOL) questionnaire about the problems faced by patients with venous thrombosis.[18] Lenchus observed that QOL decreases, following DVT events. Likewise, the occurrence of postthrombotic syndrome, which may affect 50% of those who have experienced a venous thrombosis, further negatively affects QOL and is associated with decreased activities of daily living and increased pain.[5,18,19] Lenchus explained that "33% to 55% of lower-extremity DVT patients develop postthrombotic syndrome and chronic venous insufficiency, which is characterized by pain, swelling, skin necrosis, and ulcerations."

VTE events are also associated with a substantial societal economic burden, similar to that of myocardial infarction (MI) or stroke.[20] In total, VTE events cost the US healthcare system at least $7 billion to $10 billion each year for newly diagnosed, medically treated incident cases; estimated annual healthcare costs for incident and recurrent cases of DVT or PE range from $7594 to $16,644 per patient.[21] These figures do not include penalties that may be imposed by CMS for facilities with recurrent VTE events within 30 days of hospital discharge.

Thromboprophylaxis

Although anticoagulant therapy has been used since the approval of warfarin in 1954, the VTE prophylaxis landscape has expanded significantly over the past 25 years with the approval of several new agents, including low molecular weight heparins and, more recently, direct oral anticoagulants.[22] With the surge of new medications entering the market, clinicians are challenged with not only interpreting the new drug data, but also applying new or updated guidelines and treatment strategies. These complexities have contributed to suboptimal provider adherence to thromboembolic treatment and prevention strategies.[22]

In-Hospital Prophylaxis. The benefits of anticoagulant-based thromboprophylaxis (using standard-duration VTE prophylaxis with enoxaparin for 6-14 days) in hospitalized patients at risk for developing VTE events is well established.[1] A meta-analysis from 9 clinical trials representing almost 20,000 patients found that thromboprophylaxis significantly decreased the rates of PEs, fatal PEs, and symptomatic DVTs.[23] Additionally, significant increases in major bleeding were not observed with thromboprophylaxis compared with no treatment. Despite the benefits, thromboprophylaxis is underutilized. Registry data show that only 40% to 60% of eligible hospitalized patients receive VTE prophylaxis.[1] According to the stakeholders, several reasons exist for underutilization of in-hospital VTE prophylaxis, such as decreasing hospitalization length of stay, underestimating the risk of VTE, and concerns regarding bleeding risks.[24] Rates of symptomatic VTE events in real-world studies range from 1% to 4% among at-risk acute medically ill patients, and the majority of VTE events occurred after hospital discharge (**Figure 2**).[14,25-29] Additionally, as hospital stay durations are shortening, many patients do not receive the full 6 to 14 days indicated by the guidelines.

FIGURE 2. Rates of Symptomatic VTE After Hospital Admission in Real-World Studies[14,25-29]

	Rate of Symptomatic VTE	% of VTEs Occurring Post Discharge
Amin 2012	3.3% (6 months)	57%
IMPROVE study	1.2% (3 months)	45%
Pendergraft 2013	1.1% (6 months)	57%
Mahan 2013	1.9% (3 months)	Not available
Hull 2013	3.8% (3 months)	Not available
Heit 2017	2.8% (3 months)[a]	75%

VTE indicates venous thromboembolism.
[a]282 symptomatic VTEs per 10,000 person-years

Extended-Duration Thromboprophylaxis

In the major trials supporting VTE prophylaxis in acute medically ill patients, the duration of thromboprophylaxis was 6 to 14 days.[1] Data suggests that this duration of treatment may not be sufficient for acutely ill medical patients, because the risk of experiencing VTE events remains high for the first 30 days after hospital discharge.[14,29-31]

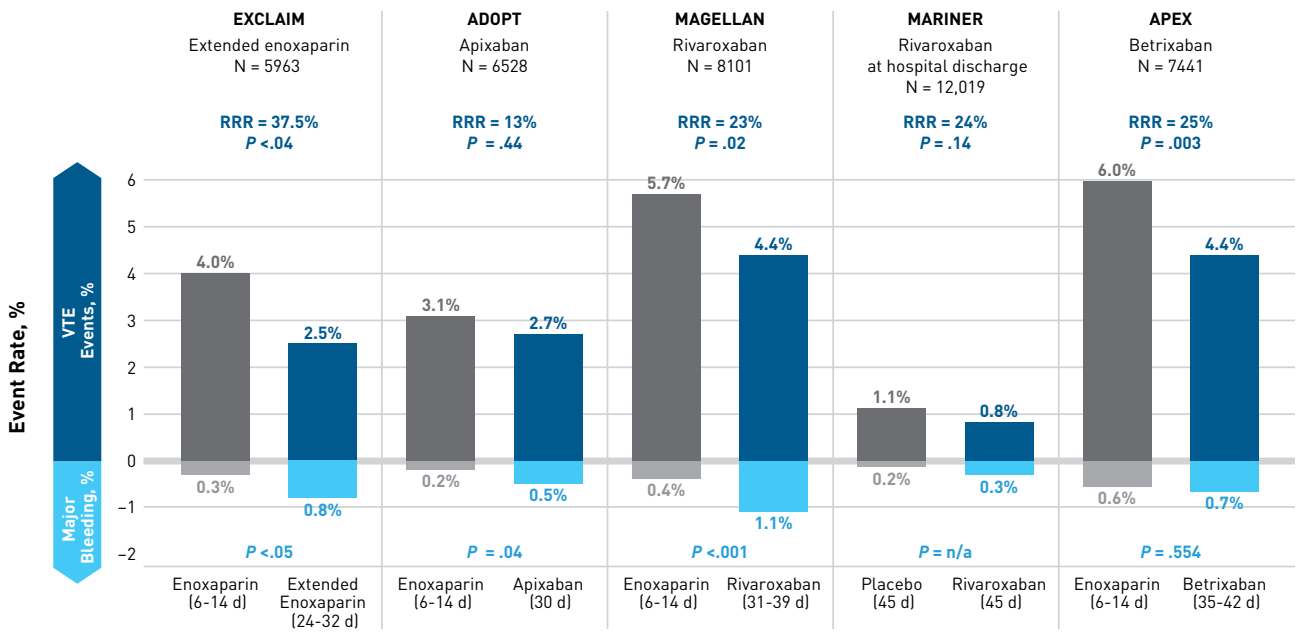
One possible reason may be that acute medically ill patients require longer duration thromboprophylaxis because they do not resume their previous level of mobility immediately following discharge from inpatient hospital settings.[1]

Another study assessed the incidence and time course of symptomatic VTE following hospitalization for medical illness. In this real-world analysis, the cumulative VTE risk over 180 days was calculated. Mean hospital length of stay was 5.3 days, and the majority of VTE events (57%) occurred after hospital discharge and standard prophylaxis completion.[14] Less than 10% of patients in this analysis received pharmacological VTE prophylaxis post discharge.[14]

Several clinical trials have evaluated the efficacy and safety of extended-duration thromboprophylaxis in acute medically ill patients (**Figure 3**).[32-37]

EXCLAIM. The randomized, parallel, placebo-controlled Extended Prophylaxis for Venous Thromboembolism in Acutely

FIGURE 3. Comparison of Extended-Duration Thromboprophylaxis Trial Data[32-37]



D indicates days; RRR, relative risk reduction; VTE, venous thromboembolism.

Ill Medical Patients with Prolonged Immobilization (EXCLAIM) trial compared extended-duration enoxaparin (28±4 days) with standard-duration VTE prophylaxis with enoxaparin (10±4 days).[32] A total of 5963 patients aged ≥40 years (mean age of 67.9 years), having an acute medical illness (eg, heart failure, respiratory disease, or infection), experiencing decreased mobility for ≥3 days before enrollment, and likely to have decreased mobility for ≥3 days after enrollment, were randomized to prophylaxis. Patients were randomized 1:1 to enoxaparin 40 mg per day subcutaneously or placebo for 28±4 days after receiving open-label enoxaparin for an initial 10±4 days. Compared with standard-duration VTE prophylaxis with enoxaparin, extended-duration enoxaparin significantly decreased the occurrence of VTE events (2.5% vs 4%, respectively; P <.04). However, major bleeding was significantly increased with extended-duration enoxaparin (0.8% vs 0.3%, respectively; P <.05).[32]

ADOPT. The randomized, double-blind, double-dummy, placebo-controlled Apixaban Dosing to Optimize Protection from Thrombosis (ADOPT) trial compared extended-duration apixaban (30 days) with standard-regimen enoxaparin (6 -14 days).[33] A total of 6528 acutely ill patients aged ≥40 years (mean age for apixaban and enoxaparin is 66.8±12.0 years and 66.7±12.0 years, respectively) who had congestive heart failure, respiratory failure, other medical disorders, ≥1 other risk factor for VTE, and who were hospitalized with an expected inpatient stay of ≥3 days were randomized to prophylaxis. Patients were randomized 1:1 to apixaban 2.5 mg orally twice daily for 30 days, or enoxaparin 40 mg per day subcutaneously for 6 to 14 days. Of the patients who could be evaluated, there were no differences between extended-duration apixaban and standard-duration VTE prophylaxis with enoxaparin regarding a 30-day composite total mortality related to VTE, PE, symptomatic DVT, or asymptomatic proximal-leg DVT. Out of all of the test subjects, 4495 (2211 in the apixaban group and 2284 in the enoxaparin group) could be evaluated for the primary efficacy outcome. Sixty patients (2.71%) in the apixaban group and 70 patients (3.06%) in the enoxaparin group met the primary efficacy outcome criteria (relative risk with apixaban, 0.87; 95% CI, 0.62 to 1.23; P = .44). By day 30, major bleeding was found to have occurred in 0.47% with extended-duration apixaban, compared with 0.19% of those receiving standard-duration VTE prophylaxis with enoxaparin.[33]

MAGELLAN. The randomized, double-blind, placebo-controlled Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban With Enoxaparin (MAGELLAN) trial compared extended-duration rivaroxaban 10 mg daily (35±4 days) with standard-duration VTE prophylaxis with enoxaparin (10±4 days).[34] A total of 8101 patients aged ≥40 years (mean age 71.0 years) who were hospitalized for an acute medical illness were randomized to prophylaxis. A primary efficacy outcome event occurred in 6.6% of patients in the rivaroxaban group and in 4.6% of those in the enoxaparin group. At day 35, an event of efficacy outcome occurred in 9.4% of those receiving extended-duration rivaroxaban

and 7.8% of patients receiving enoxaparin followed by placebo.[34] The rate of clinically relevant bleeding was significantly higher in the rivaroxaban group than the enoxaparin group (4.1% vs 1.7%, respectively). Fatal bleeding occurred in 7 patients in the extended-duration rivaroxaban group and in 1 patient in the group receiving enoxaparin followed by placebo.

MARINER. The randomized, double-blind, placebo-controlled MARINER trial evaluated the efficacy and safety of thromboprophylaxis with rivaroxaban for the prevention of symptomatic VTE events in high-risk medical patients.[35] Investigators used a modified version of the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE VTE) risk score, combined with laboratory testing, to identify eligible patients, 12,019 of which were included in the intention-to-treat analysis. The population was generally a lower risk population than other extended VTE prophylaxis studies. Upon hospital discharge, rivaroxaban was administered as 10 mg once daily for patients with creatinine clearance (CrCl) ≥ 50 ml/min; for patients having CrCl ≥30 ml/min and <50 ml/min, the dose is decreased to 7.5 mg once daily. Prophylaxis continued for 45 days, with the primary efficacy end point being the composite of symptomatic VTE (lower extremity DVT and nonfatal PE) and VTE-related deaths.

Among patients receiving rivaroxaban, 0.83% achieved the primary efficacy outcome, as compared with 1.1% of patients who were given placebo ($P = .14$). Symptomatic nonfatal VTE were identified in 0.18% of patients in the rivaroxaban group, as compared with 0.42% of patients in the placebo group (HR, 0.44; 95% CI, 0.22-0.89). Additionally, major bleeding occurred in 0.28% and 0.15% of patients in the rivaroxaban and placebo groups, respectively. The investigators concluded that, although the risk for major bleeding was low in this post-discharge population, rivaroxaban treatment was not associated with a significantly lower risk of symptomatic VTE and death, possibly due to overall low event rates.

Findings from the MARINER trial and others revealed that net clinical benefit with extended-duration thromboprophylaxis (ie, enoxaparin, apixaban, and rivaroxaban) was not observed when compared with standard-duration VTE prophylaxis with enoxaparin, mostly due to increased major bleeding events. According to the stakeholders, an unmet medical need exists for an agent in this space that is both safe and effective.

A New Option

In 2017, betrixaban was approved for the prophylaxis of VTE events in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.[36] The betrixaban approval was based on data from the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban Study (APEX) trial, which enrolled only hospitalized, acute medically ill patients who had risk factors for VTE events.[36,37] Betrixaban is currently the only approved agent indicated for VTE prophylaxis over periods of 35 to 42 days.[36]

In the APEX study, patients hospitalized for acute medical illness, were randomly assigned to 2 regimens. One group received subcutaneous placebo 'enoxaparin' for 10±4 days, plus oral betrixaban (160 mg loading dose, followed by 80 mg once daily) for 35 to 42 days. Patients having severe renal impairment or those receiving P-glycoprotein inhibitors received half dose betrixaban (80 mg loading dose, followed by 40 mg once daily). The other group received subcutaneous enoxaparin (40 mg once daily for 10±4 days) plus oral placebo 'betrixaban' for 35 to 42 days.[37] Patients with severe renal insufficiency randomized to enoxaparin received 20 mg instead of 40 mg daily. Paul P. Dobesh, PharmD, explained that the APEX study design was informed by previous studies and focused on defining acute medically ill patients at high-risk for experiencing VTE events, who would most likely benefit from extended prophylaxis. The stakeholders also noted that APEX was designed specifically for extended prophylaxis in this patient population.

Stakeholders were encouraged by the availability of an agent that can be administered over a longer time. However, they acknowledged that the issue of post-discharge risk and extended-duration therapy has yet to be addressed, and that VTE prophylaxis of any kind remains underutilized.

See the second article in this publication (page S475) for extensive analysis of the APEX trial and the role of betrixaban in the VTE prophylaxis landscape.

Treatment Guidelines for Prophylaxis

Many thromboembolic disease guidelines from major medical organizations are available:

- American College of Cardiology
- American Heart Association
- American Academy of Neurology
- American College of Chest Physicians (ACCP)
- North American Spine Society
- American Society of Clinical Oncology
- Endoscopic Surgeons
- American College of Physicians
- American Academy of Family Physicians
- Institute for Clinical Systems Improvement
- American Academy of Orthopaedic Surgeons
- Michigan Quality Improvement Consortium
- Society of American Gastrointestinal and Endoscopic Surgeons

Of these, the stakeholders report generally defaulting to the ACCP guidelines, also known as the CHEST guidelines, for VTE prophylaxis recommendations. For acutely ill hospitalized patients, the CHEST guidelines suggest anticoagulant prophylaxis with low

molecular weight heparin, low-dose unfractionated heparin (twice daily or 3 times daily), or fondaparinux.[7] According to the guidelines, thromboprophylaxis should continue for 6 to 21 days until full mobility is restored or discharge from the hospital, whichever comes first.[7] Importantly, all current guidelines were published before data from the APEX trial became available.

Because no current guidelines recommend use of VTE prophylaxis following standard-duration therapy, its use has become complicated. According to Riello and other stakeholders, the 2012 ACCP guidelines recommend against extending thromboprophylaxis beyond the period of patient immobilization or acute hospital stay in acute medically ill patients who received an initial course of thromboprophylaxis. Additionally, duration of hospital stays has broadly shortened since the results from the original studies were published. Davis went on to explain that lack of guidelines complicates International Classification of Diseases (ICD) coding. "I have read thousands of discharge summaries over the years. I have never seen on the discharge lists 'high-risk for VTE events,' because it is not a recognized code." Dobesh reiterated that the APEX trial sought to provide guidance on identifying high-risk patients. This is further discussed in the subsequent articles in this supplement.

Challenges and Complications Associated With the Use of Thromboprophylaxis

Beyond the challenges associated with guidelines for treatment, other clinical issues that complicate the use of extended VTE prophylaxis in the population under discussion include renal impairment, drug interactions, knowledge gaps, and continuity of care.

Of the currently approved direct-oral anticoagulants (DOACs), betrixaban is the least renally excreted, at <18% of absorbed drug dose (or 11% of the administered dose).[38,39] Renal excretion among other DOACs ranges from 25% to 80%.[42] Concomitant medication use with DOACs may increase the risk of major bleeding, although trials have not yet included betrixaban.[40]

Lenchus noted that acute medically ill patients also have significant comorbidities that increase the risk for drug interactions. Stakeholders observed that the various DOACs have varying pharmacokinetic profiles regarding metabolism and strongly recommended that clinicians screen patient profiles for concomitant medications that could increase bleeding risk.

Riello suggested that educational efforts in this arena are needed, as many practitioners may not be aware of the data supporting the use of thromboprophylaxis in acute medically ill patients. There was agreement among the panelists that education should be focused on improving inpatient VTE prophylaxis and adopting the continuum of care extending to post hospitalization. Panelists observed that such educational initiatives would be beneficial for providers/prescribers and prescription plans since betrixaban is the first product indicated in this setting. Jeffrey Nemeth, PharmD, MPA, explained that extended VTE prophylaxis post-hospitalization is viewed negatively at his institution because the benefits are not fully understood. Hugh Fatodu, MBA RPh, agreed that lack of utilization may be a knowledge deficit. "On the hospital side, providers and prescribers may be unwilling to address this since it is more of a chronic issue. Many systems look at acute needs, and this is simply not an acute issue," he said. As with so many other challenges in medicine, stakeholders suggested that continuity of care may also be responsible for suboptimal use of VTE prophylaxis in acute medically ill patients. According to Jacqueline Glee Lenoir, PharmD, "Medication reconciliation is still a major challenge at in many hospitals. This task, which is often initiated by a nurse in one area and completed by a nurse in a different area, is tedious and can be extremely time-consuming. Clinicians may also utilize historical data from previous admissions and rely on patients to accurately recall their medications. To further complicate the process, because fewer family practice/internal medicine physicians are admitting their patients to the hospital, high risk for VTE may not show up on their inpatient *problem list*, thus outpatient medications prescribed for this indication may not be continued."

Conclusions

Extended thromboprophylaxis represents a critical but largely unmet need for patients at risk for VTEs. The next article in this supplement explores the potential of betrixaban to address these needs. ■

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