EDITORIAL

Extended Venous Thromboembolism in Medically Ill Patients: An Unmet Need

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Of all VTE (venous thromboembolism) events that occur in the outpatient setting, roughly half are attributed to current or recent hospitalization, primarily for surgery or medical illness.[1] The time immediately following hospital discharge continues to be a period of significant VTE risk for the medically ill patient population, most notably in the first month.[2,3] Approximately 3.5 million patients appear to qualify for thromboprophylaxis after discharge from the hospital based on age > 75 or a history of cancer and while it is well understood that this risk can persist for up to 90 days after discharge, in the United States less than 5% of medically ill patients are discharged on an extended thromboprophylaxis regimen.[4,5] This can be attributed to physician decision making, lack of education and awareness of current data, and some guideline recommendations that limit VTE prophylaxis to the period of hospitalization only.[1] Medically ill patients are still affected by their disease and limited mobility post-discharge, and studies have confirmed that short-term inpatient thromboprophylaxis alone does not reduce the risk of VTE once the patient leaves the hospital.[6]

VTE occurs frequently, and prevention is critical to the overall treatment paradigm of the disease. VTE risk remains high not only for medically ill patients, but also for patients who have had a VTE event. 0.6% to 5% of patients with VTE will experience a recurrent event at 90 days and 30% will experience a recurrent event and reduced survival within 10 years.[7,8] Prevention of a future event is the cornerstone of treatment in these patients, with guidelines recommending anticoagulation therapy, specifically direct oral anticoagulants, for at least three months following a VTE event.[9] If anticoagulation therapy is prematurely stopped, risk of recurrence can reach as high as 10% in the first year in patients without reversible risk factors.[10] Transitions of care for patients diagnosed with VTE, from the hospital to home or a long-term care facility, is critical for improving patient outcomes. Organizations such as the Joint Commission and the National Quality Forum (NQF) have acknowledged that ongoing care coordination is needed for patients discharged after a VTE event.[11]

Medically ill patients are a heterogenous, challenging group that are typically older, often diagnosed with chronic obstructive pulmonary disorder (COPD), inflammatory bowel diseases, infective diseases, heart failure, ischemic stroke, or cancer and receive medications that have the potential to interact with thromboprophylaxis.[3,12] Despite the diversity in this patient population, current guidelines promote a universal, hospital-only VTE-prevention strategy, which tends to ignore the continued post-discharge risk for the

development of a VTE event.[1] This inconsistent management of VTE prophylaxis in the medically ill population has created a need for more individualized, patient-specific regimens based on their respective clinical profile and VTE and bleeding risk assessment.[1] The IMPROVE risk assessment models for VTE and bleeding are externally validated tools that can assist in identifying acutely ill medical inpatients at increased risk for VTE and bleeding. A score of $\geq$ 2 indicates increased VTE risk and a score of $\geq$ 7 indicates high bleeding risk.[1]

Ensuring that patients who are at increased risk for the development of a VTE event receive appropriate thromboprophylaxis is an important issue faced by the medical community.[12,13] A subpopulation analysis of the MAGELLAN clinical trial, which evaluated the use of rivaroxaban for extended thromboprophylaxis both in-hospital and after discharge in medically ill patients, was recently published. In the entire MAGELLAN population, patients received either rivaroxaban for extended duration (31 to 39 days) or subcutaneous enoxaparin for short duration (6 to 14 days). At 10 days, rivaroxaban demonstrated noninferiority to enoxaparin (relative risk with rivaroxaban, 0.97; 95% confidence interval [CI], 0.71 to 1.31) and at 35 days, rivaroxaban demonstrated superiority to enoxaparin for extended duration thromboprophylaxis (relative risk with rivaroxaban, 0.77; 95% CI, 0.62 to 0.96), but was associated with significantly higher clinically relevant bleeding at both timepoints.[13]

The subpopulation analysis was specifically designed to re-evaluate benefit-risk in a narrower spectrum of medically ill patients and utilized key criteria to exclude patients at highest risk of bleeding. These exclusion criteria consisted of any active gastroduodenal ulcer within 3 months of randomization or currently symptomatic, bleeding within 3 months prior to randomization or during index hospitalization prior to randomization, active cancer at randomization, medical history of severe bronchiectasis or pulmonary cavitation, and dual antiplatelet therapy at baseline.[14] Findings from the subpopulation analysis were similar to those from the original MAGELLAN population, but with key improvements in risk of major bleeding and benefit-risk balance when compared to enoxaparin and placebo. Rivaroxaban was non-inferior to enoxaparin at day 10 (relative risk with rivaroxaban, 0.82; 95% CI, 0.58 to 1.15) and superior to enoxaparin at day 35 (relative risk with rivaroxaban, 0.680; 95% CI, 0.53 to 0.88), while risk of major bleeding was reduced at both day 10 (relative risk with rivaroxaban, 1.19; 95% CI, 0.54 to 2.65) and at day 35 (relative risk with rivaroxaban, 1.48; 95% CI, 0.77 to 2.84). At day 35, rivaroxaban produced

a favorable benefit-risk balance, particularly in symptomatic VTE (non-fatal) and VTE-related death and major bleeding with a number needed to treat (NNT) of 272 and a number needed to harm (NNH) of 455.[15]

The ADOPT and EXCLAIM clinical trials also evaluated the use of extended thromboprophylaxis with apixaban and enoxaparin in medically ill patients, respectively. The ADOPT clinical trial found that extended prophylaxis with apixaban was not superior to short-term prophylaxis with enoxaparin and was associated with significantly more major bleeding events.[16] In the EXCLAIM clinical trial, extended duration thromboprophylaxis with enoxaparin reduced VTE incidence compared with placebo but increased major bleeding events.[17]

In the MAGELLAN subpopulation analysis, major and fatal bleeding rates were halved and no longer statistically significant and therefore demonstrated an improved benefit-risk profile with extended- duration prophylaxis with rivaroxaban.[15] Identifying patients at high risk of bleeding and excluding them from thromboprophylaxis treatment results in a better defined patient population that benefits from extended duration thromboprophylaxis with rivaroxaban. This MAGELLAN subpopulation analysis confirms that specific medical conditions are associated with varying levels of VTE risk, and even though VTE prophylaxis is not warranted for all patients, there are clearly groups of patients at substantial VTE risk both in the hospital and post-discharge settings who would benefit from extended duration thromboprophylaxis.[14] This analysis highlights our commitment to identifying the appropriate medically ill patient in need of outpatient VTE prophylaxis. New studies and data should explore ways to better identify patients who require VTE prophylaxis while minimizing the risk of bleeding.

Currently, Bevyxxa (betrixaban) is the only oral anticoagulant approved by the Food and Drug Administration for the prevention of VTE in acutely medically ill patients who are at risk for thromboembolic complications.[18] Approval was based on findings from the APEX trial that compared extended duration (35 to 42 days) betrixaban to short duration (6 to 14 days) subcutaneous enoxaparin. Overall, the study found that there was no difference between extended duration betrixaban and a standard regimen of enoxaparin in patients hospitalized for an acute illness with an elevated D-dimer level. Patients did, however, experience reduction in rates of symptomatic VTE and asymptomatic deep-vein thrombosis (DVT) which are linked to fatal pulmonary embolism (PE) and death in medically ill patients. An important consideration from this study is that betrixaban was not associated with significantly more major bleeding than standard duration

enoxaparin but was associated with more clinically relevant nonmajor bleeding.[19]

Clinicians and health care providers constantly strive for improved patient outcomes across the entire continuum of patient care; making treatment decisions that span a patient's clinical journey, both as an inpatient and following hospital discharge. Treatment decisions should reflect this approach and play a role in the patient's comprehensive care, throughout every step of the clinical experience. Effective in-hospital thromboprophylaxis is just the first step in the VTE treatment paradigm. More importantly, a "one size fits all" approach does not address the current medical need. Even though VTE risk factors have been identified and effective thromboprophylaxis options are available, rates of occurrence remain elevated, and VTE thromboprophylaxis post-hospital discharge remains an important unmet medical need.[7]

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