

# Reducing the burden of venous thromboembolism in the acute medically ill population with extended-duration thromboprophylaxis

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## KEYWORDS

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Hospitalized acute medically ill patients are vulnerable to venous thromboembolism (VTE), known as hospital-acquired thrombosis (HAT). The elevated risk of HAT is usually due to a combination of factors, with immobility and a prothrombotic state due to acute illness being the most frequent. The HAT risk persists well after hospital discharge, with more than half of events occurring after patient release. These HAT events may be fatal, and patients who survive the initial event may be subject to VTE recurrence, chronic discomfort from post-thrombotic syndrome and, although rare, may develop chronic thrombo-embolic pulmonary hypertension, which is often debilitating. The risk of HAT can be reduced with effective thromboprophylaxis. Current guidelines recommend thromboprophylaxis with subcutaneous heparin, low molecular weight heparin (LMWH) or fondaparinux for at-risk acute medically ill patients, but reports of real-world practice indicated that some patients do not receive protection in the short-term as outlined by the guidelines. Previous studies that have assessed extended thromboprophylaxis for 4-5 weeks with LMWH or direct oral anticoagulants in medically ill patients found they did not offer a net clinical benefit; any demonstrated efficacy was outweighed by the significantly increased risk of major haemorrhage. Therefore, there is an ongoing need for improved VTE prevention without increasing the risk of bleeding. In the APEX trial, conducted in an acute medically ill population, betrixaban provided a significant reduction in VTE events after 35 to 42 days of treatment compared with short-term enoxaparin without an increase in major bleeding.

## Understanding the risk of VTE in the acute medically ill population

Hospital-acquired venous thromboembolism (VTE), also known as hospital-acquired thrombosis (HAT), is defined as a blood clot resulting from a hospitalization, surgery, or other health care treatment; HAT can occur during hospital stay and up to 90 days post-discharge and is

considered to be a consequence of the hospitalization, disease, or treatment.<sup>1,2</sup> Acute medically ill patients are classified as patients who have been hospitalized for non-surgical problems, which include acute medical illnesses such as heart failure, ischaemic stroke, respiratory failure, other respiratory diseases, infectious disease, active cancer requiring therapy, and rheumatic and other inflammatory disease.<sup>3,4</sup> Figure 1 summarizes the estimated current rates of VTE events in the hospitalized, acute medically ill population.<sup>5</sup>

The estimated population of hospitalized acute medically ill patients at risk for HAT is over 5.5 million in an

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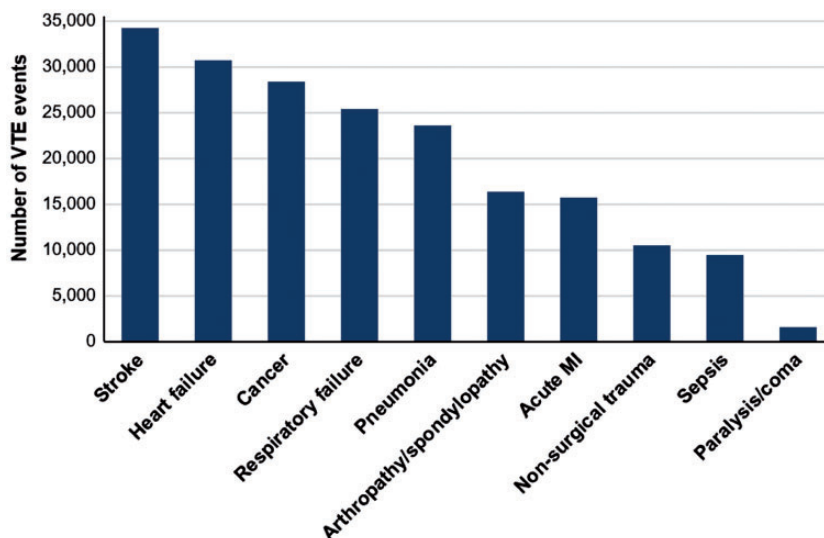


Figure 1 Estimates of venous thromboembolism (VTE) events in acute medically ill hospitalized patients.<sup>5</sup> MI, myocardial infarction.

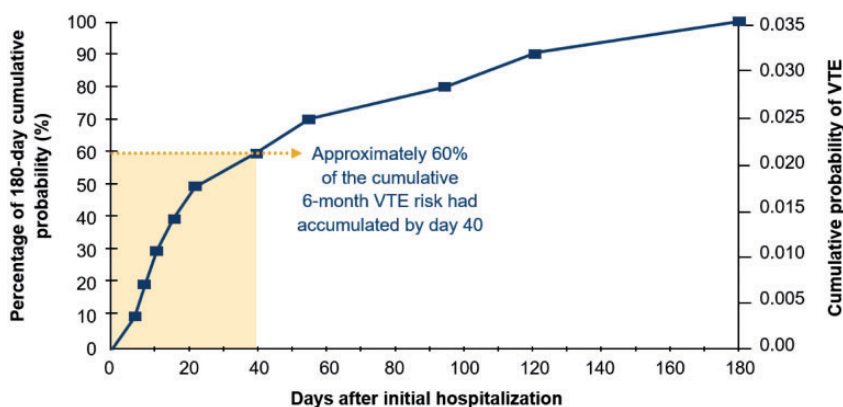


Figure 2 Cumulative risk of VTE in acute medically ill patients.<sup>7</sup>

assessment of six selected countries in the European Union (EU) and close to 8 million in the United States (US).<sup>4,6</sup> In the EU in 2007, the estimated number of VTE-related deaths per annum (543 454) was more than double the sum of deaths due to AIDS, breast cancer, prostate cancer, and transport-related fatalities.<sup>5</sup> The risk of developing VTE persists beyond discharge for some of these hospitalized, acute medically ill patients.<sup>4,7</sup> A review of multiple studies that included hospitalized medically ill patients who were not receiving thromboprophylaxis reported VTE incidence ranging from 3.65% (objectively confirmed symptomatic VTE) to as high as 17.1% (objectively confirmed symptomatic and asymptomatic events) during admission.<sup>8</sup> These results indicated that a substantial portion of hospitalized patients are at risk for developing VTE. In addition, in a large, real-world analysis of hospital claims data, it was shown that more than 50% of VTE events experienced by patients who were hospitalized for an acute illness occurred after discharge (Figure 2).<sup>7</sup> Therefore, extended duration prophylaxis for VTE in high-risk patients in both the inpatient and outpatient continuum of care remains an important clinical issue.

VTE in hospitalized acute medically ill patients is a leading but preventable cause of in-hospital morbidity and mortality in the EU and the US.<sup>9,10</sup> Those patients who do survive a VTE event may face serious and costly long-term complications, such as recurrent thromboembolism, venous insufficiency causing post-thrombotic syndrome, and chronic thrombo-embolic pulmonary hypertension.<sup>10,11</sup> A prospective study of close to 2000 patients who developed VTE confirmed that, although the risk of recurrence is highest during the first 6-12 months, the risk remains, even after more than a decade past the initial event.<sup>12</sup> Patients with a neurological condition that required hospitalization when the initial thrombotic event occurred had an 3.5-fold increased risk of recurrence.<sup>12</sup> Another systematic review of prospective cohort studies and randomized trials of patients with a first episode of symptomatic VTE found that at 24 months after stopping anticoagulant therapy, the rate of recurrence was 3.3% per patient-year for all patients who had a transient risk factor (e.g. recent surgery or pregnancy); the subgroup with a non-surgical risk factor had a risk of recurrence of 4.2% per patient.<sup>13</sup> For the group of patients who had an unprovoked

VTE (a VTE with no apparent clinical risk factor), the rate of recurrence was 7.4% per patient-year.<sup>13</sup> These results suggest that there is an elevated risk of recurrence within 24 months of the initial VTE for patients with non-surgical risk factors and those with an unprovoked initial event. The elevated risk of recurrence in patients with ongoing non-surgical risk factors was further confirmed by the findings from the EINSTEIN choice study.<sup>14</sup> With regard to long-term effects of a VTE event, patients may suffer a diminished quality of life following a VTE due to the development of post-thrombotic syndrome due to chronic venous insufficiency. If untreated, the patient may be subject to lifelong conditions characterized by pain, swelling, skin changes of pigmentation and eczema, and in the worst cases, venous ulceration.<sup>11,15</sup>

To fully grasp the importance of thromboprophylaxis, an understanding of why acute medically ill patients are at risk for VTE development is pertinent. Virchow's Triad consists of three broad categories of events that can contribute to the development of a venous thrombosis: hypercoagulability, reduction in flow, and endothelial perturbation or injury.<sup>2</sup> Risk factors of VTE generally contribute to one or more of the categorical events listed in Virchow's Triad. Patients with acute medical illnesses are at increased risk for developing a VTE due to the inflammatory nature of their acute medical illness such that it induces a prothrombotic state, and/or as a consequence of prolonged immobility during the illness and convalescence. Known risk factors for VTE in hospitalized medical patients include immobility, active malignancy, history of VTE, acute infectious and inflammatory disease, obesity, increasing age (especially those aged >70 years), the use of the combined oral contraceptive pill and hormone replacement therapy, heart and/or respiratory failure, certain drugs, as well as inherited and acquired thrombophilias and sickle cell disease.<sup>16,17</sup>

Medically ill patients are also often at risk for bleeding, and this risk must be carefully balanced against the risk of thrombosis in these patients.<sup>18</sup> Balancing these clinical considerations can be particularly challenging within the elderly patient population, since advanced age is a risk factor for both VTE and bleeding events.<sup>18</sup> Elderly patients, patients with very low body weight, and patients with renal impairment require careful dosing of anticoagulants. Dosing considerations, adjustments or caps are often required for anticoagulants in these special populations.<sup>19</sup> A number of risk assessment models have been developed to aid in stratifying hospitalized medical patients according to VTE risk to identify appropriate treatment candidates.<sup>18</sup> However, there is no internationally standardized risk assessment tool recommended for use with medically ill patients at this time.<sup>18</sup> Likewise, there are no bleeding risk assessment models that are satisfactorily validated.

### Short-term thromboprophylaxis in acute medically ill patients

Effective thromboprophylaxis for VTE in acute medically ill patients remains an unmet need.<sup>10,11</sup> Historically, the concept of routine thromboprophylaxis in medically ill patients

was considered controversial, despite the regular use of such practices for surgical patients.<sup>20</sup> However, this changed with the advent of randomized controlled trials using low molecular weight heparin (LMWH) or fondaparinux vs. placebo in medical patients. In the randomized, double-blind, placebo-controlled MEDENOX study, hospitalized medically ill patients deemed at risk for HAT received either subcutaneous enoxaparin (20 mg or 40 mg) or placebo for 6-14 days to assess the efficacy and safety of enoxaparin thromboprophylaxis for the prevention of deep-vein thrombosis (DVT) and pulmonary embolism (PE).<sup>20</sup> The incidence of VTE by Day 14 was significantly lower in the cohort treated with 40 mg enoxaparin compared with the placebo-treated group [5.5% vs. 14.9%, respectively; relative risk (RR) 0.37; 97.6% confidence interval (CI) 0.22-0.63;  $P < 0.001$ ]; this protective benefit was maintained for an additional 3 months.<sup>20</sup> A low risk of major haemorrhage was observed for enoxaparin vs. placebo as well.<sup>20</sup> In the PREVENT study, treatment with a once daily subcutaneous injection of 5000 IU dalteparin for 14 days resulted in a 45% reduction of risk of a composite endpoint of VTE and VTE-related sudden death compared with placebo in hospitalized, immobilized, acute medically ill patients ( $P = 0.0015$ ) with a low risk of major bleeding.<sup>21</sup> This therapeutic benefit was maintained for 90 days.<sup>21</sup> The benefits of short-term thromboprophylaxis in acute medically ill patients were further supported by the results from the ARTEMIS study. In ARTEMIS, an older medically ill population (mean age  $\approx 75$  years) was randomized to receive 2.5 mg fondaparinux or placebo within 48 h of hospital admission, and treatment continued once daily until Days 6 through 14.<sup>22</sup> Treatment with fondaparinux almost halved the rate of VTE in this older medically ill patient population, with a minimal risk of major bleeding complications (RR reduction 46.7%; 95% CI 7.7%-69.3%;  $P = 0.029$ ).<sup>22</sup> Enoxaparin dose reduction is required for patients with severe renal impairment [creatinine clearance (CrCl) = 15-30 mL/min], and careful clinical monitoring without dose adjustment is advised for patients with moderate (CrCl = 30-50 mL/min) and mild (CrCl = 50-80 mL/min) renal impairment.<sup>23</sup> Fondaparinux is contraindicated in patients with severe renal impairment (CrCl < 20 mL/min), and dose reduction is required for patients with CrCl = 20-50 mL/min. Fondaparinux should be used with caution in patients who are elderly or have low body weight (<50 kg).<sup>24</sup>

The results from MEDENOX,<sup>20</sup> PREVENT,<sup>21</sup> and ARTEMIS<sup>22</sup> trials helped lay the foundation for short-term thromboprophylaxis guidelines in this patient population. For acutely ill, hospitalized, immobilized patients at increased risk of thrombosis, current guidelines suggest anticoagulant thromboprophylaxis with LMWH, low-dose unfractionated heparin twice daily or three times daily, or fondaparinux until full mobility is restored or until discharge from hospital.<sup>17</sup> Thromboprophylaxis is only recommended for at-risk patients who have one or more of the risk factors mentioned above.<sup>17</sup> However, thromboprophylaxis is rarely administered for the recommended duration in real-world practice. An analysis of administrative claims data and hospital billing data in the US for over 11 000 hospitalized medically ill patients found that mean duration of

VTE prophylaxis was only 5 days, which may be insufficient for high-risk patients.<sup>7</sup> Another analysis of multiple studies shows that up to 62% of hospitalized patients who would benefit from thromboprophylaxis were not offered any preventative treatment.<sup>8</sup> The multinational cross-sectional ENDORSE study, which examined whether nearly 70 000 surgical and medical patients who received adequate thromboprophylaxis during hospitalization if they were deemed to be at risk for VTE, found that only half of those at-risk patients received American College of Chest Physicians (ACCP)-recommended prophylactic treatment.<sup>25</sup> In the UK, the National Institute for Health and Care Excellence (NICE) implemented VTE risk assessment guidelines in 2010, and financial sanctions were introduced by National Health Service (NHS) England at the same time for hospitals that do not adhere to the 95% threshold for VTE risk assessment for all inpatient services.<sup>26,27</sup> Since the program's inception, there has been a significant reduction in HAT, a 15% reduction in VTE events attributed to insufficient thromboprophylaxis, and a decrease in VTE-associated mortality.<sup>28</sup> However, this systematic approach to HAT prevention, while much admired, has not been duplicated elsewhere. Despite thromboprophylaxis guidelines being in place, globally many patients who are at risk for VTE are still being woefully undertreated.

### Extended thromboprophylaxis in acute medically ill patients: first attempts

Would medically ill patients who are at high risk for VTE derive benefit from thromboprophylaxis that extends beyond the recommended guidelines? The MEDENOX researchers issued a call to action for future studies to examine whether prolonging prophylaxis in this patient population would provide additional benefit, as it was shown to do in surgical patients after two fatal pulmonary emboli occurred in the MEDENOX study several weeks after thromboprophylaxis was discontinued.<sup>20</sup> The EXCLAIM trial evaluated extended duration thromboprophylaxis with enoxaparin vs. placebo in acute medically ill patients who experienced a recent reduction in mobility.<sup>29</sup> All patients ( $n = 6085$ ) received open-label subcutaneous enoxaparin 40 mg for  $10 \pm 4$  days; patients were then entered into the double-blind portion of the trial and randomized to either continue enoxaparin or placebo for an additional  $28 \pm 4$  days.<sup>29</sup> Extended duration enoxaparin significantly reduced the rate of VTE events vs. placebo [2.5% vs. 4.0%; absolute risk difference  $-1.53\%$  (95.8% CI  $-2.54\%$  to  $-0.52\%$ )], but the rate of major haemorrhages at 30 days was significantly greater in the extended-duration enoxaparin group compared with placebo [0.8% vs. 0.3% events, respectively; absolute risk difference 0.51% (95% CI 0.12-0.89%)]. Although this study found a benefit for extended thromboprophylaxis with enoxaparin in certain patient subgroups, i.e., those with Level 1 immobility, those older than 75 years, and women, the findings did not support the use of extended enoxaparin prophylaxis in the broader medically ill population due to an unfavourable benefit-to-risk ratio due to the risk of major bleeding events.<sup>29</sup>

The advent of direct oral anticoagulants (DOACs) initially provided promise for extended prophylaxis in the outpatient setting due to their more convenient method of oral administration, but a net clinical benefit had not been demonstrated until the APEX trial, which is discussed at length later in this supplement. In ADOPT, 6528 medically ill patients were randomized to receive either oral apixaban 2.5 mg b.i.d. for 30 days or subcutaneous enoxaparin 40 mg once a day for 6-14 days with matching placebos, to determine whether long-term prophylaxis against VTE with apixaban would be safer and more effective than short-term treatment with enoxaparin.<sup>30</sup> The primary efficacy outcome (composite during the 30-day treatment period of death related to VTE (i.e., sudden death for which PE could not be excluded as a cause), fatal or non-fatal PE, symptomatic DVT, or asymptomatic proximal-leg DVT as detected with the use of systematic bilateral compression ultrasonography) occurred in 2.7% of patients who received apixaban and 3.1% of those who received short-term enoxaparin prophylaxis (RR with apixaban 0.87; 95% CI 0.62-1.23;  $P = 0.44$ ).<sup>30</sup> Although the rate of symptomatic VTE was lower among apixaban-treated patients compared with enoxaparin-treated patients, this difference did not reach statistical significance. From a safety perspective, long-term apixaban treatment was associated with significantly more major bleeding events than the short-term enoxaparin treatment in this patient population (RR with apixaban 2.58; 95% CI 1.02-7.24;  $P = 0.04$ ).<sup>30</sup> Given that the extended course of treatment with apixaban did not offer improved thromboprophylaxis compared with enoxaparin and was also associated with major bleeding, the ADOPT trial did not provide justification for extended thromboprophylaxis with apixaban after discharge in medically ill patients.

The MAGELLAN trial also compared extended prophylaxis in acute medically ill patients ( $n = 8101$ ) who were randomized to receive either oral rivaroxaban 10 mg QD for  $35 \pm 4$  days, or a 6- to 14-day course of subcutaneous enoxaparin 40 mg QD, plus matching placebos.<sup>31</sup> Extended treatment with rivaroxaban met the pre-specified endpoint for non-inferiority at the Day 10 data analysis; 2.7% of rivaroxaban-treated patients and 2.7% of enoxaparin-treated patients experienced a primary outcome event (composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic non-fatal PE, or death related to VTE); RR with rivaroxaban 0.97; 95% CI 0.71-1.31;  $P = 0.003$ .<sup>31</sup> At Day 35, the rate of the primary efficacy outcome measure was significantly lower with rivaroxaban than with enoxaparin (4.4% vs. 5.7%, respectively; RR with rivaroxaban 0.77; 95% CI 0.62-0.96;  $P = 0.02$ ). However, there was a significant increase in treatment-related major and clinically relevant non-major bleeding both during Days 1 through 10 (rivaroxaban 2.8% vs. enoxaparin 1.2%; RR 2.3; 95% CI 1.63-3.17;  $P < 0.001$ ) and Days 1 through 35 (rivaroxaban 4.1% vs. enoxaparin 1.7%; RR 2.5; 95% CI 1.85-3.25;  $P < 0.001$ ).<sup>31</sup> At Day 35, 1.1% of rivaroxaban-treated patients and 0.4% of enoxaparin-treated patients experienced major bleeding (RR with rivaroxaban 2.9%; 95% CI 1.60-5.15;  $P < 0.001$ ). Therefore, the modest improvement in thromboprophylaxis with

extended rivaroxaban treatment vs. enoxaparin cannot be justified due to an increased risk of bleeding events.

Collectively, these data do not support extended thromboprophylaxis with enoxaparin, apixaban, or rivaroxaban in medically ill patients, and none of these agents have been approved by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) for extended use. Long-term studies did not support extended use of enoxaparin, and the method of administration (subcutaneous injection) is a potential barrier for treatment adherence in the post-discharge setting. Conversely, DOACs have a more convenient route of oral administration. Notwithstanding, those newer oral anticoagulants in use before the APEX trial did not offer adequate protection without increasing the risk of haemorrhage. Therefore, the need persists to protect this vulnerable patient population from VTE after discharge, without increasing the risk of bleeding.

### Betrixaban for long-term thromboprophylaxis in acute medically ill patients

Betrixaban is a new, oral, potent factor Xa inhibitor with a different pharmacokinetic profile than other commercially available DOACs. Betrixaban was recently approved by the FDA in the US for the prevention of VTE in acute medically ill patients based upon the findings from a large, randomized, double-blind, double-dummy, active-controlled, multinational clinical trial: Acute Medically Ill VTE Prevention With Extended Duration Betrixaban (APEX).<sup>3</sup> The APEX trial randomized >7500 patients to receive either subcutaneous enoxaparin (10 ± 4 days) or oral betrixaban (35–42 days) plus matching placebos. Building upon the body of research presented earlier, the study population in APEX was carefully selected to include acute medically ill patients who were at an increased risk of VTE but who also had a lower risk of bleeding when compared with the patient populations from past studies.<sup>32</sup> For betrixaban, the study demonstrated a significant reduction in VTE events after 35 to 42 days of treatment compared with short-term enoxaparin, without increase in major bleeding, in acute medically ill patients.<sup>3,33</sup> Symptomatic events (symptomatic DVT, non-fatal PE, or VTE-related death) were experienced by 0.9% of patients treated with betrixaban compared with 1.5% of patients treated with enoxaparin in the modified intent-to-treat (mITT) population.<sup>33</sup> Only 3.6% of betrixaban-treated patients had an asymptomatic event, detected by ultrasound, vs. 4.7% of enoxaparin-treated patients.<sup>33</sup> Major bleeding was detected in 0.67% of patients treated with betrixaban vs. 0.57% of patients treated with enoxaparin.<sup>33</sup> In contrast with other DOACs, the betrixaban US label supports use of betrixaban in patients with severe renal impairment (Stage IV chronic kidney disease classification; creatinine clearance 15–29 mL/min), provided that the betrixaban dose is reduced to 40 mg.<sup>33</sup> This is the first study to demonstrate an overall net benefit for extended thromboprophylaxis in the acute medically ill patient population. The results from APEX are discussed in detail in the Beyer-Westendorf *et al.* 2018 article in this supplement and suggest that the

incorporation of betrixaban into clinical practice may finally address the longstanding unmet need for extended thromboprophylaxis in the vulnerable acute medically ill population.

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