



# Proportion of US Hospitalized Medically Ill Patients Who May Qualify for Extended Thromboprophylaxis

Clinical and Applied  
Thrombosis/Hemostasis  
Volume 25: 1-6  
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DOI: 10.1177/1076029619850897  
journals.sagepub.com/home/cat



Benjamin Miao, PharmD<sup>1,2</sup>, Bhavana Chalupadi, PharmD<sup>1</sup>,  
Brendan Clark, PharmD<sup>1</sup>, Alexis Descoteaux, PharmD<sup>1</sup>,  
Daniel Huang, PharmD<sup>1</sup>, Sabrina Ilham, PharmD<sup>1</sup>,  
Brian Ly, PharmD<sup>1</sup>, Alex C. Spyropoulos, MD<sup>3,4,5</sup>,  
and Craig I. Coleman, PharmD<sup>1,2</sup>

## Abstract

Extended thromboprophylaxis with oral anticoagulation can reduce the risk of symptomatic venous thromboembolism (VTE) in high-risk patients. We sought to estimate the proportion of medically ill patients in the United States who might qualify for extended thromboprophylaxis according to the criteria used in the Medically-Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-Discharge Venous ThromboEmbolic Risk (MARINER) trial. We analyzed 2014 National Inpatient Sample (NIS) data that provide a 20% weighted annual sample of all discharges from US acute-care hospitals. Hospitalizations for acute medically ill patients were identified as those with a primary discharge diagnosis code for heart or respiratory failure, ischemic stroke, infection, or inflammatory diseases. Patients were excluded if they were <40 years old, admitted for surgery or trauma, had a length of stay <3- or >35-days, or were contraindicated to nonvitamin K antagonist oral anticoagulants. The modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE)-VTE score was used to stratify patients' risk for postdischarge VTE, with a score of 2 to 3 suggesting patients were at moderate- and  $\geq 4$  as high-risk. Of the 35 358 810 hospitalizations in the 2014 NIS, 1 849 535 were medically ill patients admitted for heart failure (10.1%), respiratory failure (12.2%), ischemic stroke (8.8%), infection (58.5%), or inflammatory diseases (10.4%). The modified IMPROVE-VTE score classified 1 186 475 (64.1%) of these hospitalizations as occurring in moderate-risk and 407 095 (22.0%) in high-risk patients. This real-world study suggests a substantial proportion of acute medically ill patients might benefit from extended thromboprophylaxis using the modified IMPROVE-VTE score and clinical elements of the MARINER trial.

## Keywords

anticoagulants, factor Xa inhibitors, hospitalization, medically ill, venous thromboembolism

Date received: 26 February 2019; revised: 09 April 2019; accepted: 23 April 2019.

## Introduction

Patients with an acute medical illness such as pneumonia, stroke, or congestive heart failure are highly susceptible to the development of venous thromboembolism (VTE) during their hospital stay and up to 3-months postdischarge.<sup>1,2</sup> Randomized controlled trials (RCTs).<sup>3-6</sup> suggest that high-risk medically ill patients can reduce their risk of symptomatic VTE by initiating thromboprophylaxis in-hospital and continuing extended thromboprophylaxis for up to 6 weeks postdischarge but at the potential cost of additional bleeding.<sup>7</sup> The trials randomized acute medically ill patients  $\geq 40$  years of age but used different strategies to target high-risk populations, such as D-dimers and

<sup>1</sup> Department of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, CT, USA

<sup>2</sup> Hartford Hospital Evidence-Based Practice Center, Hartford, CT, USA

<sup>3</sup> The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

<sup>4</sup> The Feinstein Institute for Medical Research, Manhasset, NY, USA

<sup>5</sup> Department of Medicine, Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, New York, NY, USA

## Corresponding Author:

Craig I. Coleman, University of Connecticut School of Pharmacy, UCONN/ Hartford Hospital, Evidence-Based Practice Center, 80 Seymour Street, Hartford, CT 06102, USA.

Email: craig.coleman@hhchealth.org



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risk scores. At present, it is unclear what proportion of medically ill patients warrant extended thromboprophylaxis. A better understanding of the proportion and characteristics of medically ill patients who may qualify for extended thromboprophylaxis will allow health care decision makers to better understand the potential costs/expenditure needed to provide such an intervention as well as to estimate potential downstream costs savings from preventing VTE. Therefore, we sought to estimate the proportion of hospitalizations in medically ill patients in the United States that might qualify for extended thromboprophylaxis according to clinical criteria used in the Medically Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-Discharge Venous Thromboembolism Risk (MARINER) trial for identifying an at-VTE risk group.<sup>5</sup>

## Methods

This study utilized the 2014 Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project National Inpatient Sample (NIS).<sup>8</sup> The NIS is among the largest publicly available inpatient databases in the United States and approximates a 20% sample of discharges from hospitals across the country. National Inpatient Sample covers Medicare, Medicaid, privately insured, and uninsured patients, and contains data on patient and hospital demographics and billing codes (up to 30 *International Classification of Diseases-Ninth Revision (ICD-9)* diagnosis, 15 *ICD-9* procedural codes and corresponding Clinical Classifications Software [CCS] diagnosis, and procedure code groupings) per encounter. No laboratory or medication utilization data are available in the NIS, including availability of D-dimer testing. The 2014 inpatient core file contains data on 35 358 810 hospitalizations occurring between January 1, 2014, and December 31, 2014, drawn from 4411 hospitals across 44 states.

This analysis defined candidacy for extended thromboprophylaxis as being a medically ill patient at sufficient risk according to the criteria utilized in the MARINER trial (which evaluated rivaroxaban vs placebo for extended thromboprophylaxis).<sup>5</sup> The MARINER trial criteria were chosen (vs other RCT criteria) due to greater ease of implementation in an administrative claims database. All eligibility criteria were identified using provided demographics or *ICD-9* diagnosis, procedural or CCS-based coding. Eligibility criteria included a hospitalization for a medically ill patient  $\geq 40$  years of age with a primary billing code for decompensated heart failure, respiratory failure, infection, ischemic stroke, or inflammatory disease (including rheumatic diseases), survival to discharge, and a duration of hospitalization  $\geq 3$  but  $\leq 35$  days.<sup>3-5</sup> Hospitalizations for major surgical procedures, occurring in patients with a comorbidity requiring full-dose anticoagulation (eg, admission for VTE, history of atrial fibrillation or heart valve replacement) or with a prior history of clinically-relevant bleeding, trauma, or injury or a contraindication to a nonvitamin K oral anticoagulant (NOAC; eg, coagulopathy, liver disease, alcohol abuse, acquired immunodeficiency syndrome, sustained uncontrolled hypertension, or severe renal insufficiency) were excluded from this analysis.

Hospitalizations for medically ill patients meeting the above-mentioned criteria were further risk stratified using the modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score to be consistent with the MARINER study design.<sup>5,9</sup> The modified IMPROVE risk score uses age ( $\geq 60$  years), complete immobilization or sedentary with or without bathroom privileges for  $\geq 1$  day (assumed present in everyone for this study), prior VTE, history of cancer, thrombophilia or lower limb paralysis, as well as the need for an intensive or critical care unit stay (hospitalization coded for sepsis, respiratory, or acute decompensated heart failure) to assess patients' risk of subsequent VTE (area under the curve = 0.72).<sup>10</sup> Patients with a score  $\geq 4$  were deemed high risk, 2 to 3 at moderate risk, and  $\leq 1$  at low risk of VTE up to 3 months after admission. The modified IMPROVE score differs from the original in its definition of immobility (immobilization lasting for  $\geq 1$  day vs  $\geq 7$  days) and the inclusion of patients with either active or a prior history of cancer versus a history of cancer only. A sensitivity analysis in which we applied the original IMPROVE score immobility criteria of  $\geq 7$  days (also the approximate mean length of stay in the MARINER trial population)<sup>5</sup> was performed.

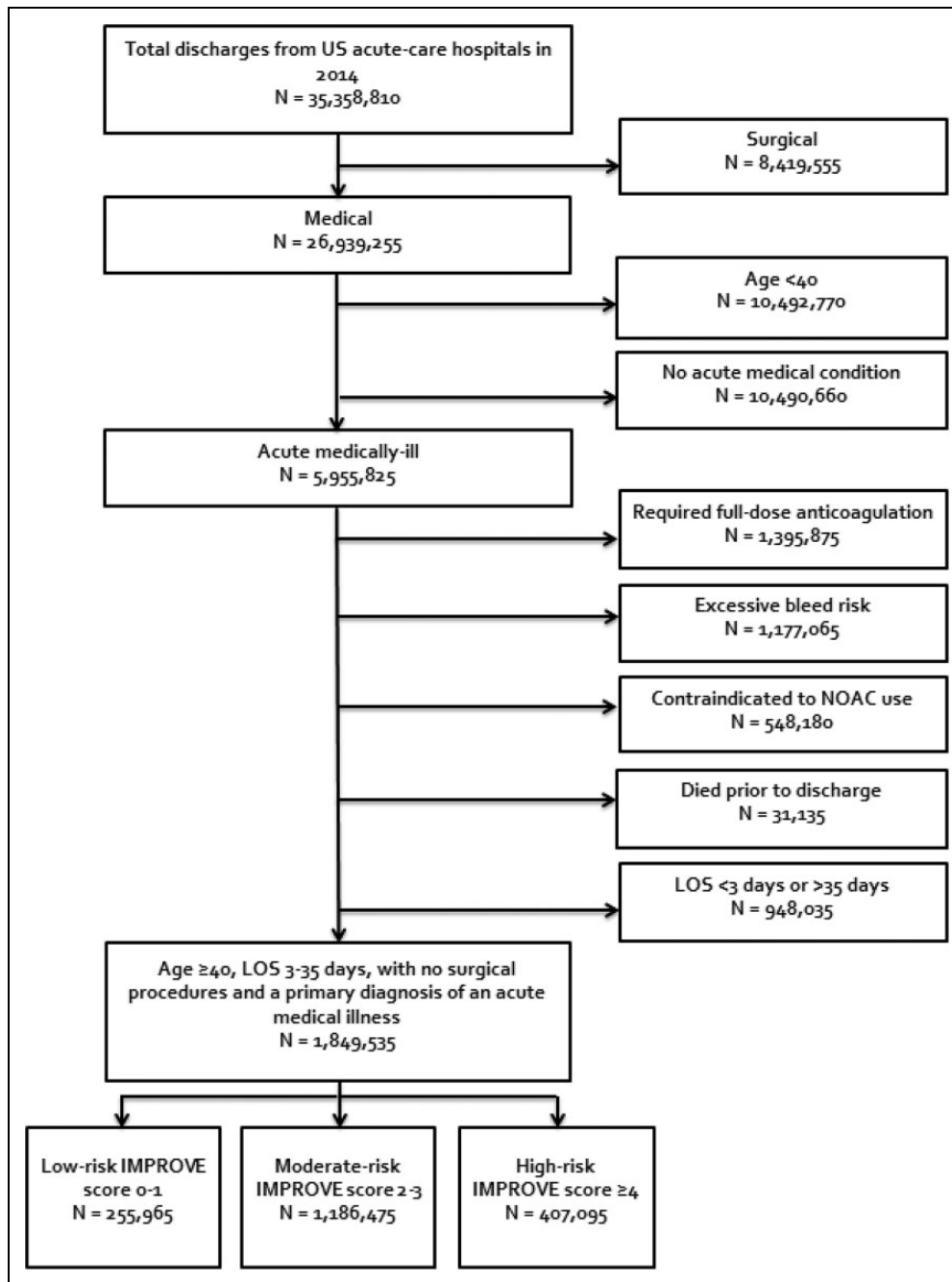
Categorical data were reported as percentages, while continuous data were summarized as medians with 25%, 75% ranges. All data management was performed using IBM SPSS Statistics version 25.0 (IBM Corp, Armonk, New York). As this analysis was only performed on data that were deidentified and in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality, it was deemed exempt from institutional review board oversight.

## Results and Discussion

In total, 35 358 810 hospital discharges were captured in the 2014 NIS data set (Figure 1). We excluded 10 492 770 (29.7%), 10 490 660 (29.7%), and 8 419 555 (23.8%) hospitalizations because patients were less than 40 years of age, lacked the required medical conditions, or had a primary code for a surgical procedure, respectively. We then excluded 1 395 875 (3.9%), 1 177 065 (3.3%), 979 170 (2.8%), and 548 180 (1.6%) hospitalizations because patients were ineligible for extended thromboprophylaxis due to the need for full-dose anticoagulation, high-risk of bleeding, hospital length of stay  $< 3$  or  $> 35$  days, or ending in death or had a likely contraindication to NOAC use, respectively.

This left 1 849 535 discharges for patients with an acute medical illness meeting initial MARINER criteria (Table 1). The most frequent reasons for admission included acute infection (58.5%), respiratory failure (12.2%), and heart failure (10.1%). Upon risk stratification, 407 095 (22.0%) were calculated as having a modified IMPROVE score  $\geq 4$  (high-risk), 1 186 475 (64.2%) a score of 2 to 3 (moderate-risk), and the remaining 255 965 (13.8%) having a score of 1 or less (low-risk).

Our study provides a real-world estimate of the proportion of hospitalizations in the United States associated with patients



**Figure 1.** Flow of study inclusion and exclusion. IMPROVE, indicates International Medical Prevention Registry on Venous Thromboembolism; LOS, length-of-stay; N, number of hospitalizations; NOAC, nonvitamin k oral anticoagulant.

who might qualify for extended thromboprophylaxis. Unlike randomized trials<sup>3-5</sup> that are performed in select centers and only include patients who agree to be studied, the utilized NIS data set<sup>8</sup> had millions of hospitalizations and data are likely more representative of the US population. We found that 22.0% of hospitalized acute medically ill patients in the 2014 NIS data set are at high risk of VTE according to the modified IMPROVE VTE score from the MARINER trial criteria,<sup>5,9</sup> and thus might benefit from extended thromboprophylaxis after discharge. Another 64.2% of hospitalized acute medically ill

patients were found to be at moderate risk, requiring D-dimer testing to determine their suitability for extended thromboprophylaxis.<sup>5</sup> Compared to the IMPROVE registry<sup>10</sup> which found 7% of medical inpatients to have a score of  $\geq 4$  (high-risk; and 25% a score of 2-3 [moderate-risk]), our study indicated a larger proportion of medically ill patients (22%) may be at high risk of VTE. The reason for the greater proportion of high-risk patients identified in our study versus the IMPROVE registry may be a result of our use of age  $\geq 40$  and not 18 years of age as in IMPROVE registry and our defining immobility as

**Table 1.** Characteristics of Hospitalizations in the 2014 National Inpatient Sample, Stratified by Thrombosis Risk.

	All, n (%)	Low-Risk, n (%)	Moderate-Risk, n (%)	High-Risk, n (%)
Number of discharges	1 849 535	255 965	1 186 475	407 095
Demographics				
Age, years (median, 25%, 75% range)	70 (58, 81)	51 (46, 55)	72 (62, 83)	73 (64, 83)
Female sex	1 081 935 (58.5%)	149 875 (58.6%)	708 640 (59.7%)	223 420 (54.9%)
Length of stay, days (median, 25%, 75% range)	4 (3, 6)	4 (3, 5)	4 (3, 6)	5 (3, 7)
Race				
White	1 268 520 (68.6%)	165 675 (64.7%)	808 455 (68.1%)	294 390 (72.3%)
African American	264 585 (14.3%)	43 135 (16.9%)	168 410 (14.2%)	53 040 (13.0%)
Hispanic	148 445 (8.0%)	26 465 (10.3%)	97 140 (8.2%)	24 840 (6.1%)
Asian or Pacific Islander	36 710 (2.0%)	3050 (1.2%)	26 645 (2.2%)	7015 (1.7%)
Native American	10 205 (0.6%)	1865 (0.7%)	6750 (0.6%)	1590 (0.4%)
Other	43 740 (2.4%)	6875 (2.7%)	28 495 (2.4%)	8370 (2.1%)
Missing	77 330 (4.2%)	8900 (3.5%)	50 580 (4.3%)	17 850 (4.4%)
Qualifying primary medical diagnosis				
Heart failure	186 530 (10.1%)	145 (0.1%)	152 160 (12.8%)	34 225 (8.4%)
Respiratory failure	225 110 (12.2%)	56 810 (22.2%)	133 030 (11.2%)	35 270 (8.7%)
Infection	1 081 805 (58.5%)	148 075 (57.8%)	667 575 (56.3%)	266 155 (65.4%)
Ischemic stroke	162 445 (8.8%)	0 (0%)	132 440 (11.2%)	30 005 (7.4%)
Inflammatory/rheumatic disorder	193 645 (10.4%)	50 935 (19.9%)	101 270 (8.5%)	41 440 (10.1%)
Modified IMPROVE VTE risk factors <sup>a</sup>				
History of VTE (3 points)	110 875 (6.0%)	-	0 (0%)	110 875 (27.2%)
Thrombophilia (2 points)	7535 (0.4%)	-	790 (0.1%)	6745 (1.7%)
Cancer (2 points)	336 855 (18.2%)	-	30 800 (2.6%)	306 055 (75.2%)
Lower limb paralysis (2 points)	28 980 (1.6%)	-	5685 (0.5%)	23 295 (5.7%)
ICU/CCU stay (1 point)	901 390 (48.7%)	-	679 510 (57.3%)	221 880 (54.5%)
Age $\geq$ 60 years (1 point)	1 318 610 (71.3%)	-	975 395 (82.2%)	343 215 (84.3%)

Abbreviations: CCU, critical care unit; ICU, intensive care unit; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; VTE, venous thromboembolism.

<sup>a</sup>Value in () represent points assigned in the modified IMPROVE score.

a duration of hospital stay  $\geq$ 1-day as opposed to the  $\geq$ 7-day value used in the IMPROVE registry. Importantly, both age and immobilization risk were risk factors assigned a point in the modified IMPROVE score. Moreover, the additional inclusion of an elevated D-dimer level as a risk factor for moderate-risk patients makes direct comparison of our results to that of the IMPROVE registry difficult.

There are 4 main trials supporting the benefit of extended thromboprophylaxis with NOACs in patients hospitalized with an acute medical illness. The Apixaban Dosing to Optimize Protection from Thrombosis (ADOPT) trial<sup>6</sup> randomized acute medically ill patients (n = 6528)  $\geq$ 40 years of age who had restricted mobility and additional risk factors (such as previous VTE, cancer, or obesity) to apixaban 2.5 mg twice daily for 30 days or enoxaparin 40 mg once daily for at least 6 days while in the hospital. Apixaban did not significantly reduce the primary composite end point of VTE-related death, pulmonary embolism (PE), and symptomatic or asymptomatic VTE detected through ultrasonography (2.71% vs 3.06%; relative risk, 0.87; 95% confidence interval [CI] = 0.62-1.23; *P* = .44). 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>3</sup> randomized patients (n = 8101)  $\geq$ 40 years of age who were

hospitalized for an acute medical illness to rivaroxaban 10 mg once daily for 35  $\pm$  4 days or enoxaparin 40 mg once daily for 10  $\pm$  4 days. At day 35, the rivaroxaban group showed a significant reduction in the primary composite outcome of total VTE and VTE-related death (4.4% vs 5.7%; relative risk, 0.77; 95% CI = 0.62-0.96; *P* = .02). Medically-Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-Discharge Venous ThromboEmbolic Risk<sup>5</sup> randomized medically ill patients (n = 12 019)  $\geq$ 40 years of age who were at an increased risk for VTE (identified using D-dimer and the IMPROVE VTE risk stratification tool) to rivaroxaban 10 mg once daily or placebo for 45-days postdischarge. The rivaroxaban group insignificantly reduced the primary composite outcome of symptomatic VTE and VTE-related death versus placebo (0.83% vs 1.10%; hazard ratio, 0.76; 95%CI = 0.52-1.09; *P* = .14) while significantly decreasing patients hazard of symptomatic VTE events alone compared to placebo (0.18% vs 0.42%; hazard ratio, 0.44; 95%CI = 0.22-0.89). Medically-Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-Discharge Venous ThromboEmbolic Risk employed an overly broad definition of VTE-related death, including sudden deaths in which PE could not be ruled out in the primary composite outcome. The Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) trial<sup>4</sup> randomized medically ill patients (n = 7513)  $\geq$ 40 years of age who were at

an increased risk of VTE (identified using D-dimer and advancing age) to betrixaban 80 mg once daily for 35 to 42 days or enoxaparin 40 mg once daily for  $10 \pm 4$  days. Betrixaban did not significantly reduce the primary end point of total VTE and VTE-related death in the primary population but significantly reduced the primary end point in the overall population (4.4% vs 6.0%; relative risk, 0.75; 95%CI = 0.61-0.91;  $P = .003$ ). Based on the APEX data, betrixaban is currently the only Food and Drug Administration–approved NOAC for prolonged thromboprophylaxis in medically ill patients.<sup>11</sup>

The criteria used for determining the need for extended thromboprophylaxis is relatively similar across the MAGELLAN,<sup>3</sup> APEX,<sup>4</sup> MARINER,<sup>5</sup> and ADOPT<sup>6</sup> trials. Each used an age  $\geq 40$  years, presence of acute medical illness, and tested a duration of NOAC therapy ranging from 35 to 45 days. Each trial<sup>3-5</sup> used an acute medical illness definition consisting of heart failure, respiratory failure, acute infection, inflammatory/rheumatic disorder, and acute ischemic stroke. Certain exclusion criteria present in MARINER, such as active cancer, cardiogenic or septic shock requiring vasopressor support, severe bronchiectasis, and cavitary tuberculosis, were not applied in this study because they were used as a risk factor in the modified IMPROVE score, not consistently utilized as exclusion criteria in other RCTs of extended duration thromboprophylaxis or amounted to an insignificant portion of the population ( $<0.1\%$ ). All 3 trials also included similar added VTE risk factors including the presence of advanced age, history of VTE, cancer (active or history of), thrombophilia, as well as immobility criteria. We utilized the MARINER<sup>5</sup> criteria using the IMPROVE VTE score<sup>9</sup> in our study, as it was the most amendable to implementation in claims data. However, the MARINER criteria<sup>5</sup> and the APEX criteria<sup>4</sup> for extended thromboprophylaxis required data on D-dimer levels ( $\geq 2x$  the upper limit of normal), which are not available in claims data sets such as the NIS.<sup>8</sup> Based on modified IMPROVE VTE scores,<sup>9</sup> we were able to identify a high-risk subpopulation that should receive extended thromboprophylaxis per the clinical criteria in MARINER<sup>5</sup> and a subpopulation that was at low-risk and should not be offered therapy regardless of their D-dimer values (and so levels should not be ordered). We also identified a substantial population at moderate risk of VTE that would require D-dimer concentrations to discern their suitability for extended thromboprophylaxis. Given continued thromboprophylaxis may increase clinically relevant bleeding risk, D-dimer testing is warranted in this subpopulation. Of note, 47.6% of the study population in MAGELLAN<sup>3,12</sup> had elevated D-dimer concentrations  $\geq$  twice the upper limit of normal, while in the MARINER trial,<sup>5</sup> 70.4% of patients had the same threshold of an elevated D-dimer. Unfortunately, it is unclear if the presence of an elevated D-dimer meeting threshold criterion was evenly distributed across the various risk categories in these trials.<sup>3-5</sup> Thus, we estimate that at least 22% of all hospitalized acute medically ill patients in our sample might have qualified from extended thromboprophylaxis based on clinical criteria alone.

Our study has several additional limitations worth noting. First, biases such as misclassification can negatively impact the internal validity of claims database analyses.<sup>13</sup> Second, NIS does not contain robust data on immobility,<sup>8</sup> and there are typically substantial issues in the evaluation of immobility status in clinical studies (including interobserver variability in severity assessment and a lack of standardized definitions). The MAGELLAN<sup>3</sup> and APEX<sup>4</sup> trials defined immobility as being confined to a bed or chair for the majority of the day, with independent mobility only to the in-room toilet for at least 24-hours. The MARINER trial<sup>5</sup> used current lower limb paralysis or paresis, which is defined as a leg falling to the bed within 5 seconds but with the limb able to impart effort against gravity. In our study, all patients with a hospital length of stay for  $\geq 3$  days were considered immobile. Of note, our use of hospitalization for  $\geq 3$  days as a surrogate for immobility in this study may have resulted in an overestimation of patient risk. To address this concern, we performed a sensitivity analysis raising the cutoff to  $\geq 7$ -days which resulted in 14.6% (as compared to 22% in the base case) of hospitalized acute medically ill patients being classified as high risk and 43.2% (compared to 64.2%) at moderate risk. However, we believe our a priori definition of immobility (more consistent with the modified IMPROVE score) is more likely to be accurate, as studies suggest immobility tends to be front loaded (occurring in the first 24-48 hours) of a hospital admission.<sup>14</sup> Finally, we used NIS data so that our conclusion may be less generalizable to non-US populations with acute medical illness requiring hospitalization.<sup>8,12</sup>

## Conclusion

This real-world study suggests that there is a substantial population of acute medically ill patients who would benefit from extended thromboprophylaxis using the modified IMPROVE VTE score and clinical elements of the MARINER trial criteria.

## Authors' Note

B. Miao and C. I. Coleman each provided substantial input into the design and conduct of the study, and analysis and interpretation of its results. B. Chalupadi, B. Clark, A. Descoteaux, D. Huang, S. Ilham, and B. Ly contributed substantially to the study conduct and analysis of data. B. Miao, C. I. Coleman, and A.C. Spyropoulos were primarily responsible for critically reviewing and revising this manuscript, but all authors contributed to the revision of the intellectual content and approved the final version of the manuscript to be published.


## Declaration of Conflicting Interests


The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Coleman has served as a consultant for Boehringer Ingelheim, Janssen Scientific Affairs, Bayer AG, and Portola. Dr Spyropoulos has served as a consultant for Boehringer Ingelheim, Janssen, Bayer Healthcare, and Daiichi Sankyo and has served on advisory committees for Bristol-Myers Squibb, Pfizer, Janssen, Portola, and Bayer Healthcare.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## ORCID iD

Benjamin Miao  <https://orcid.org/0000-0002-2550-5027>

Craig I. Coleman  <https://orcid.org/0000-0003-4868-7158>

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