Rivaroxaban for extended thromboprophylaxis in acutely ill medical patients 75 years of age or older

Walter Ageno1 | Renato D. Lopes2 | Mark Goldin3 | Roger D. Yusen4 |
Gregory W. Albers5 | Gregory C. Elliott6 | Jonathan L. Halperin7 | William R. Hiatt8 |
Gregory Maynard9 | Philippe Gabriel Steg10 | Jeffrey I. Weitz11 | Eunyoung Suh12 |
Wentao Lu12 | Elliott S. Barnathan12 | Gary E. Raskob13 | Alex C. Spyropoulos3,14

1Department of Medicine and Surgery, University of Insubria, Varese, Italy
2Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA
3Department of Medicine, Anticoagulation and Clinical Thrombosis Services Northwell Health at Lenox Hill Hospital, The Feinstein Institute for Medical Research and Zucker School of Medicine at Hofstra/Northwell, New York, NY, USA
4Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO, USA
5Director Stanford Stroke Center, Stanford Medical Center, Stanford University, Palo Alto, CA, USA
6Departments of Medicine, University of Utah and Intermountain Healthcare, Salt Lake City, UT, USA
7Cardiovascular Institute, Mount Sinai Medical Center, New York, NY, USA
8Division of Cardiology, University of Colorado School of Medicine, and CPC Clinical Research, Aurora, CO, USA
9University of California at Davis, Sacramento, CA, USA
10Université de Paris, Assistance Publique-Hôpitaux de Paris, INSERM U-1148, Paris, France
11McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada
12Cardiovascular Clinical Development, Janssen Research and Development, LLC, Raritan, NJ, USA
13Hudson College of Public Health, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
14Department of Obstetrics and Gynecology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

Abstract

Background: Although older patients are at increased risk for venous thromboembolism (VTE), thromboprophylaxis is underused because of bleeding concerns. The MARINER trial evaluated whether rivaroxaban reduced symptomatic postdischarge VTE in acutely ill medical patients.

Objectives: We hypothesized that rivaroxaban would have a favorable benefit/risk profile in patients ≥75 years of age.

Methods: Patients were randomized in a double-blind manner at hospital discharge to rivaroxaban (10 mg/day for creatinine clearance ≥50 ml/min; 7.5 mg/day for ≥30-<50 ml/min) or placebo for 45 days. Using a Cox proportional hazard model including treatment as a covariate, we compared the risk of the primary efficacy outcome...
INTRODUCTION

Acutely ill medical patients are at increased risk for venous thromboembolism (VTE), and this risk may persist after resolution of the acute illness. International guidelines recommend pharmacologic prophylaxis with unfractionated heparin, low molecular weight heparin, or fondaparinux during hospitalization for an acute medical illness, but not after hospital discharge because of the uncertain benefit of extended treatment. Two recent randomized clinical trials with the direct oral anticoagulants (DOACs) betrixaban and rivaroxaban identified higher risk medically ill patients who benefit from prophylaxis extended for up to 45 days. These results led to regulatory approval of these DOACs in the United States for thromboprophylaxis in medically ill patients.

Patients at increased risk for VTE at the time of hospital discharge may be identified by assessment of individual VTE risk factors, use of a risk assessment model such as the IMPROVE VTE score, and by determination of the D-dimer level during hospitalization. Advanced age, especially ≥75 years, represents one of the key independent risk factors for VTE in acutely ill medical patients. However, the risk of bleeding also increases with increasing age. Therefore, the benefit/risk profile of anticoagulation needs to be assessed carefully in elderly patients.

MARINER was a randomized, double-blind trial that compared once-daily oral rivaroxaban 10 mg (7.5 mg if creatinine clearance was between 30 and 49 ml/minute) with placebo for 45 days. Patients were enrolled at the time of hospital discharge and identified using a modified IMPROVE score and plasma D-dimer levels. Although the primary efficacy outcome of symptomatic VTE and VTE-related death was not significantly reduced by rivaroxaban in comparison to placebo, a significant reduction in symptomatic VTE and major and fatal vascular events was observed. The incidence of major bleeding was low in both groups.
rivaroxaban or placebo in a 1:1 ratio (stratified by renal function into a 10-mg stratum and a 7.5-mg stratum) and treatment was initiated. To be eligible, patients had to be 40 years of age or older and hospitalized for specific acute medical illnesses, such as heart failure, respiratory insufficiency, stroke, and infectious or inflammatory diseases for at least 3 but no more than 10 consecutive days before randomization. Eligible patients also were required to have other risk factors for VTE that were demonstrated by a total modified IMPROVE VTE risk score ≥4 or VTE risk score of 2 or 3 with D-dimer >2× the upper limit of normal. Patients with an increased risk of bleeding (eg, those with bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy, active gastroduodenal ulcer or any bleeding in prior 3 months) were excluded from the study.

The primary hypothesis of the MARINER study was that rivaroxaban was superior to placebo for the prevention of the composite outcome of symptomatic VTE (lower extremity deep vein thrombosis, nonfatal pulmonary embolism [PE]), and VTE-related death (death from PE or death in which PE could not be ruled out as the cause).

The primary hypothesis of the present exploratory analysis was that rivaroxaban would have a favorable benefit/risk profile in patients ≥75 years of age consistent with that observed in those younger than 75 years of age. All secondary outcomes included in the MARINER study were also compared in the two age groups.

### 2.2 Efficacy and safety outcomes

The primary efficacy outcome (composite of symptomatic VTE and VTE-related death) was analyzed in the intention-to-treat population and compared between treatment groups in patients ≥75 and <75 years of age. The principal safety outcome of major bleeding was based on the International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria and included fatal bleeding, bleeding into a critical organ, or bleeding that led to a decrease in hemoglobin of ≥2 g/dl or transfusion of 2 or more units of whole blood or packed red blood cells. ISTH major bleeding was assessed in the on-treatment (plus 2 days) safety population. Secondary efficacy included: 1) VTE-related death; 2) symptomatic VTE; 3) symptomatic VTE plus all-cause mortality; 4) the composite of symptomatic VTE, myocardial infarction, ischemic stroke, and cardiovascular death; and 5) all-cause mortality. An additional safety outcome was nonmajor clinically relevant bleeding events (NMCRB). Cardiovascular death was defined as death from a known cardiovascular cause or death in which a cardiovascular cause, including pulmonary embolism, could not be ruled out. NMCRB was defined as overt bleeding that did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, temporary cessation of the trial regimen, or pain with impairment of activities of daily life. All endpoints were adjudicated by a blinded clinical events committee.

### 2.3 Statistical methods

In this prespecified subgroup analysis, we used a Cox proportional hazard model that included treatment as a covariate to compare the risks of the primary efficacy and safety outcome events as well as each secondary outcome event rate in patients aged ≥75 years old and those <75 years old who were randomly assigned to rivaroxaban or placebo in the overall study population and in the 10-mg stratum. The Kaplan-Meier method was used to estimate risk differences over time. Additional analyses were performed using the subgroups of <65 years and ≥65 years and are provided in the Tables S1–S3.

### 3 RESULTS

#### 3.1 Baseline characteristics

Baseline clinical and demographic characteristics were assessed in patients ≥75 and <75 years of age in the overall intention-to-treat population (receiving either rivaroxaban or matching placebo). A total of 4294 patients were ≥75 years of age and 7725 patients were <75 years of age. In the group of patients ≥75 years of age, there were fewer males (43.5% vs. 57.2%, respectively); mean body weight was lower (75.4 kg vs. 83.7 kg); and the percentages of patients with D-dimer >2 times the upper limit of normal (76.7% vs. 66.9%) and with moderate renal insufficiency (38.4% vs. 7.1%) were higher than in those <75 years of age (Table 1).

#### 3.2 Primary efficacy outcome

The incidence of the primary efficacy outcome was 2-fold higher in patients ≥75 than in those <75 years of age (Table 2). There was a numerically lower incidence of primary outcome events in both age groups with rivaroxaban compared with placebo (≥75 years of age: 1.2% and 1.6%, respectively; HR 0.73, 95% CI 0.43-1.22; <75 years of age: 0.6% and 0.8%, HR 0.78, 95% CI 0.46-1.32; the interaction p-value for age group was .85). Similar results were observed in the 10-mg stratum in those ≥75 years of age (rivaroxaban 0.9% vs. placebo 1.6%, HR 0.56, 95% CI 0.28-1.14); the interaction p-value for age group was .54 (Figure 1).

#### 3.2.1 Primary safety outcome

The incidence of major bleeding was low in both age groups, with no significant treatment interaction (≥75 years of age: 0.3% and 0.1% with rivaroxaban and placebo, respectively; HR 3.45, 95% CI 0.72-16.61; <75 years of age: 0.3% and 0.2%, respectively; HR 1.44, 95% CI 0.55-3.77; the interaction p-value for age group was .35). Similar results were observed in the rivaroxaban10-mg stratum (≥75 years of age: 0.3% and 0.2%, respectively; HR 1.30, 95% CI 0.48-3.48; the interaction p-value for age group was .69).
3.3 | Secondary efficacy outcomes

Venous thromboembolism-related death occurred in 1.0% (rivaroxaban) and 1.1% (placebo) of patients in the ≥75 years of age group (HR 0.95, 95% CI 0.53-1.71) and in 0.5% and 0.6%, respectively, in the <75 years of age group (HR 0.91, 95% CI 0.50-1.65); the interaction p-value for age group was .92. The results in the rivaroxaban 10-mg stratum were similar (≥75 years of age: 0.9% and 1.0%, HR 0.91, 95% CI 0.41-1.99); the interaction p-value for age group was .98.

In both age groups, symptomatic VTE was numerically lower with rivaroxaban compared with placebo, occurring in 0.3% and 0.7%, respectively, in the ≥75 years of age group (HR 0.43, 95% CI 0.16-1.11) and in 0.1 and 0.3, respectively, in the <75 years of age group (HR 0.46, 95% CI 0.16-1.31); the interaction p-value for age was .92. In the rivaroxaban 10-mg stratum, there was a nominally
significant lower incidence of symptomatic VTE in the age ≥75 group with rivaroxaban compared with placebo: 0.1% and 0.7% respectively, HR 0.11, 95% CI 0.01-0.86; the interaction p-value for age group was .20.

In the ≥75 years of age group, symptomatic VTE and all-cause mortality occurred in 1.9% and 2.3% of patients receiving rivaroxaban and placebo, respectively (HR 0.81, 95% CI 0.54-1.23) and in 1.0% and 1.5%, respectively, in the <75 years of age group (HR 0.65, 95% CI 0.43-0.98); the interaction p value for age group was .45. In the rivaroxaban 10-mg stratum, the results were similar (≥75 years of age: 1.4% vs. 2.1% respectively, HR 0.69, 95% CI 0.38-1.24); the interaction p-value for age group was .84.

The incidence of the composite outcome of symptomatic VTE, myocardial infarction, ischemic stroke, and cardiovascular death was higher in patients ≥75 years of age compared with those <75 years of age. These incidences were 2.1% with rivaroxaban and 2.8% with placebo (HR 0.75, 95% CI 0.51-1.11) in patients ≥75 years of age and 1.3% and 1.6%, respectively (HR 0.81, 95% CI 0.56-1.17) in patients <75 years of age; the interaction p value for age group was .79. In the rivaroxaban 10-mg stratum, in patients ≥75 years of

### TABLE 2  Efficacy and safety endpoints in MARINER by age and treatment group

| Efficacy (ITT)                                             | Age <75 years |                          | Age ≥75 years |                          | HR and 95% CIs |
|-----------------------------------------------------------|---------------|---------------------------|---------------|---------------------------|---------------|
|                                                           | Rivaroxaban   | Placebo                   | Rivaroxaban   | Placebo                   |               |
|                                                           | N = 3853 (%)  | N = 3872 (%)              | N = 2154 (%)  | N = 2140 (%)              |               |
| Overall population                                        |               |                           |               |                           |               |
| Primary efficacy outcome                                  | 25 (0.6)      | 32 (0.8)                  | 25 (1.2)      | 34 (1.6)                  | 0.73 (0.43-1.22) |
| Symptomatic VTE                                           | 5 (0.1)       | 11 (0.3)                  | 6 (0.3)       | 14 (0.7)                  | 0.43 (0.16-1.11) |
| VTE-related death                                         | 21 (0.5)      | 23 (0.6)                  | 22 (1.0)      | 23 (1.1)                  | 0.95 (0.53-1.71) |
| Symptomatic VTE and all-cause mortality                   | 37 (1.0)      | 57 (1.5)                  | 41 (1.9)      | 50 (2.3)                  | 0.81 (0.54-1.23) |
| Composite of symptomatic VTE, MI, ischemic stroke, and cardiovascular death | 50 (1.3)      | 62 (1.6)                  | 44 (2.0)      | 58 (2.7)                  | 0.75 (0.51-1.11) |
| All-cause mortality                                       | 33 (0.9)      | 48 (1.2)                  | 38 (1.8)      | 41 (1.9)                  | 0.92 (0.59-1.44) |

| Safety (safety set)                                       | Rivaroxaban   | Placebo                   | Rivaroxaban   | Placebo                   | HR and 95% CIs |
|-----------------------------------------------------------|---------------|---------------------------|---------------|---------------------------|---------------|
|                                                           | N = 3837 (%)  | N = 3855 (%)              | N = 2145 (%)  | N = 2125 (%)              |               |
| Overall population                                        |               |                           |               |                           |               |
| ISTH major bleeding                                       | 10 (0.3)      | 7 (0.2)                   | 7 (0.3)       | 2 (0.1)                   | 3.45 (0.72-16.61) |
| Non-major clinically relevant bleeding                    | 55 (1.4)      | 32 (0.8)                  | 30 (1.4)      | 19 (0.9)                  | 1.54 (0.87-2.74) |

| Safety (safety set)                                       | Rivaroxaban   | Placebo                   | Rivaroxaban   | Placebo                   | HR and 95% CIs |
|-----------------------------------------------------------|---------------|---------------------------|---------------|---------------------------|---------------|
|                                                           | N = 3561 (%)  | N = 3589 (%)              | N = 1329 (%)  | N = 1301 (%)              |               |
| 10-mg stratum                                             |               |                           |               |                           |               |
| ISTH major bleeding                                       | 9 (0.3)       | 7 (0.2)                   | 4 (0.3)       | 2 (0.2)                   | 1.95 (0.36-10.67) |
| Non-major clinically relevant bleeding                    | 47 (1.3)      | 29 (0.8)                  | 26 (2.0)      | 12 (0.9)                  | 2.10 (1.06-4.17) |

Abbreviations: ITT, intention to treat; MI, myocardial infarction; VTE, venous thromboembolism.
The incidence of all-cause mortality in patients receiving rivaroxaban and placebo were 1.8% and 1.9%, respectively, in the ≥75 years of age group (HR 0.92, 95% CI 0.59-1.44) and 0.9% and 1.2%, respectively, in the <75 years of age group (HR 0.69, 95% CI 0.44, 1.07); the interaction p-value for age group was .36. In the rivaroxaban 10-mg stratum, the incidence of all-cause mortality in patients ≥75 years of age was 1.4% vs. 1.5%, respectively (HR 0.93, 95% CI 0.50-1.75; the interaction p-value for age group was .44).

3.4 | Secondary safety outcome

The incidence of NMCRB also was similarly low for the two age groups, but in patients <75 years of age, the difference between rivaroxaban and placebo was statistically significant ≥75 years of age: 1.4% and 0.9% with rivaroxaban and placebo, respectively (HR 1.54, 95% CI 0.87-2.74). In those <75 years of age the incidences were 1.4% and 0.8%, respectively (HR 1.73, 95% CI 1.12-2.67; the interaction p-value for age was .76). In the rivaroxaban 10-mg stratum, NMCRB occurred more frequently in the rivaroxaban group than in the placebo group in those ≥75 years of age: 2.0% and 0.9%, respectively (HR 2.10, 95% CI 1.06-4.17; the interaction p-value for age group was .55).

3.5 | Benefit/risk profile over time

To address the benefits and risks of treating patients 75 years of age and older who are at increased risk of both thrombotic events and bleeding, we used the Kaplan-Meier method to determine the risk differences over time in a hypothetical population of 10 000 patients treated with rivaroxaban or placebo who were 75 years of age and older in the overall population (Figure 2A) and in the 10-mg stratum (Figure 2B). As shown in both populations, the benefits in preventing primary outcome events continue to accumulate over time and exceed the number of major bleeding events caused. This finding was more pronounced in the 10-mg stratum. The risk differences for all outcomes for <75, ≥75, <65, and ≥65-year-old subgroups are provided in Table S3. In general, the results in the ≥65-year-old subgroup for all of the efficacy and safety results were similar to the ≥75-year-old subgroup (Table S2).

4 | DISCUSSION

In the MARINER trial, about one-third of medically ill patients at risk for VTE were 75 years of age or older. For these older patients, the rate of symptomatic VTE and VTE-related death, the primary efficacy outcome of the MARINER trial, was nearly double that in patients younger than 75 years of age, but the relative risk reduction for extended rivaroxaban thromboprophylaxis vs. placebo was similar in the two age groups, and there was no statistical evidence of interaction with age group. Similar trends were observed for all secondary efficacy outcomes, including cardiovascular events. Major bleeding and NMCRB rates were low with no statistically significant interaction with age.

Older age, especially ≥75 years, has been consistently associated with an increased risk of VTE in acutely ill medical patients, and it is also proposed as one of the key factors either independently or as part of validated VTE risk scores to identify patients who may benefit from extended thromboprophylaxis after hospital discharge.8,11 Clinical trials investigating the benefit of extended anticoagulant prophylaxis in high-risk medical patients have reported conflicting results. Two recently published meta-analyses of these trials reported a 39% relative risk reduction in symptomatic VTE and VTE-related death12 and a 27% decreased risk of symptomatic nonfatal PE and VTE-related death,13 respectively. These benefits, however, came at a cost of a 2-fold increase in major bleeding12 and a nonsignificant 40% increase in the risk of critical site or fatal bleeding.13 These findings have raised the concern that an excess of bleeding events could offset the benefit of extended thromboprophylaxis in older patients.
Results from the EXCLAIM trial found a net clinical benefit of extended enoxaparin vs. placebo in patients >75 years of age, which reflected a greater reduction in the risk of VTE in the elderly and a similar increase in major bleeding in the two treatment arms. In a subgroup analysis of older patients enrolled in the APEX trial, the relative risk reduction in the composite of the primary efficacy and primary safety endpoints obtained with betrixaban was similar in those ≥80 years of age and those younger than 80 years of age, with no significant interaction across age groups. As in the present analysis of the MARINER trial, the relative risk reduction in the primary efficacy endpoint in patients 80 years of age or older was similar to that in younger patients (22% and 26%, respectively), with no significant interaction across age groups. Major bleeding rates in the APEX trial were nonsignificantly higher in the group 80 years or older treated with extended duration betrixaban (1.1%) than in patients treated with enoxaparin (0.5%), whereas these rates were similar between treatment groups in patients younger than 80 years of age (0.4% vs. 0.6%, p = .39). Again, no significant interaction across age groups was observed. Overall, these results are consistent with the results presented in this analysis of MARINER and suggest a favorable benefit/risk ratio for extended thromboprophylaxis with DOACs for elderly patients at high risk for VTE after hospitalization for an acute medical illness.

Recent studies of VTE prevention have included major cardiovascular events as secondary efficacy outcomes. One substudy of the APEX trial reported that extended thromboprophylaxis with betrixaban significantly reduced all-cause mortality and ischemic stroke compared with standard duration thromboprophylaxis, and a second substudy reported a significant reduction of irreversible and fatal events. In a prespecified subanalysis of MARINER, extended thromboprophylaxis with the 10-mg dose of rivaroxaban showed a significant reduction in major and fatal vascular events through 45 days. In the present study, we observed higher rates of major and fatal vascular events in patients 75 years or older than in those less than 75 years of age, and a similar reduction with extended rivaroxaban thromboprophylaxis (including both the 10-mg and 7.5-mg doses) between the two age groups, with no significant age-related interactions. The results were similar when the 10-mg dose group only was considered. When benefits and risks were explored over

![Figure 2](https://example.com/figure2.png)
time in both the overall population and in those in the 10-mg stratum, the benefits in terms of primary efficacy events prevented were numerically greater than the major bleeding events caused over time (Figure 2). Given the increased risk of cardiovascular events in the elderly, these results corroborate the benefit/risk profile of extended thromboprophylaxis in this subgroup of patients.

The results of this study should be interpreted with caution given that the study did not stratify by age and subgroup analyses were not powered to detect statistically significant differences between treatment arms. However, our prespecified subgroup analysis has several strengths including the double-blind design of the primary study, the rigorous methodology used for outcomes assessment, and the large sample of older patients enrolled.

In conclusion, symptomatic VTE and VTE-related death rates in acutely ill medical patients were nearly 2-fold higher in the elderly patients (age 75 years or greater) compared with nonelderly patients. The benefit of rivaroxaban, particularly at 10 mg daily, in reducing such events as well as major cardiovascular events without a significant increase in major bleeding observed in the whole MARINER trial population seems confirmed in the subgroup of patients aged 75 years or older. The benefit/risk profile of rivaroxaban in patients ≥75 years of age appears consistent with that observed in the general population.

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CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS
All authors have contributed equally to the manuscript: (1) conception and design of the work, analysis and interpretation of the data; (2) drafting the work or revising it critically for important intellectual content including: Introduction, Methods, Results, Discussion; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that the questions related to the accuracy and integrity of any part.

ORCID
Jeffrey I. Weitz  https://orcid.org/0000-0002-1092-7550

REFERENCES
1. Hull RD, MeraI T, Mills A, Stevenson AL, Liang J. Venous thrombembolism in elderly high-risk medical patients: time course of events and influence of risk factors. Clin Appl Thromb Haemost. 2013;19:357-362.
2. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv. 2018;2:3198-3225.
3. Cohen AT, Harrington RA, Gibson CM. Betrixaban in acutely ill medical patients. N Engl J Med. 2016;375:e50.
4. Spyropoulos AC, Ageno W, Albers GW, et al. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. N Engl J Med. 2018;379:1118-1127.
5. Raskob GE, Spyropoulos AC, Zrubeck J, et al. The MARINER trial of rivaroxaban after hospital discharge for medical patients at high risk of VTE. Design, rationale, and clinical implications. Thromb Haemost. 2016;115(6):1240-1248.
6. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010;8:2450-2457.
7. Spyropoulos AC, Anderson FA Jr, FitzGerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010;8:2450-2457.
8. Cohen AT, Alikhan R, Arcelus JI, et al. Assessment of venous thromboembolism risk and the benefits of thromboprophylaxis in medical patients. Thromb Haemost. 2005;94(4):750-759.
9. Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest. 2011;139:69-79.
10. Spyropoulos A, Ageno W, Albers G, et al. Post-discharge prophylaxis with rivaroxaban reduces fatal and major thromboembolic events in medically ill patients. J Am Coll Cardiol. 2020;75:3140-3147.
11. Spyropoulos AC, Ageno W, Cohen AT, Gibson CM, Goldhaber SZ, Raskob G. Prevention of venous thromboembolism in hospitalized medically ill patients: a US perspective. *Thromb Haemost*. 2020;120:924-936.

12. Bajaj NS, Vaduganathan M, Qamar A, et al. Extended prophylaxis for venous thromboembolism after hospitalization for medical illness: a trial sequential and cumulative meta-analysis. *PLoS Med*. 2019;16(04):e1002797.

13. Chiasakul T, Evans CR, Spyropoulos AC, Raskob G, Crowther M, Cuker A. Extended vs. standard-duration thromboprophylaxis in acutely ill medical patients: a systematic review and metaanalysis. *Thromb Res*. 2019;184:58-61.

14. Yusen RD, Hull RD, Schellong SM, et al. Impact of age on the efficacy and safety of extended-duration thromboprophylaxis in medical patients. *Thromb Haemost*. 2013;110:1152-1163.

15. Ageno W, Lopes RD, Yee MK, et al. Net-clinical benefit of extended prophylaxis of venous thromboembolism with betrixaban in medically ill patients aged 80 or more. *J Thromb Haemost*. 2019;17:2089-2098.

16. Gibson CM, Chi G, Halaby R, et al. Extended duration betrixaban reduces the risk of stroke versus standard dose enoxaparin among hospitalized medically ill patients: an APEX trial substudy. *Circulation*. 2017;135:648-655.

17. Gibson CM, Korjian S, Chi G, et al. Comparison of fatal or irreversible events with extended-duration betrixaban versus standard dose enoxaparin in acutely ill medical patients: an APEX trial substudy. *J Am Heart Assoc*. 2017;6:6.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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