Rivaroxaban Plus Aspirin for Extended Thromboprophylaxis in Acutely Ill Medical Patients: Insights from the MARINER Trial

Alex C. Spyropoulos1,2, Mark Goldin3, Walter Ageno4,5, Gregory W. Albers6, C. Gregory Elliott7, William R. Hiatt8,9, Jonathan L. Halperin10, Gregory Maynard11, P. Gabriel Steg12, Jeffrey I. Weitz13,14, Theodore E. Spiro15, Wentao Lu16, Jessica Marsiglio16, Gary E. Raskob17, Elliot S. Barnathan16

The Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell, The Feinstein Institute for Medical Research, New York, New York, United States
2 Department of Medicine, Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, New York, New York, United States
3 Northwell Health, Great Neck, New York, United States
4 Department of Medicine and Surgery, University of Insubria, Varese, Italy
5 University of Insubria, Varese, Italy
6 Stanford Stroke Center, Stanford Medical Center, Stanford University, Palo Alto, California, United States
7 Department of Medicine, University of Utah and Intermountain Healthcare, Salt Lake City, Utah, United States
8 Division of Cardiology, University of Colorado School of Medicine
9 CPC Clinical Research, Aurora, Colorado, United States
10 Cardiovascular Institute, Mount Sinai Medical Center, New York, New York, United States
11 University of California at Davis, Sacramento, California, United States
12 Université de Paris, Assistance Publique–Hôpitaux de Paris, and INSERM U-1148, Paris, France
13 McMaster University
14 The Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada
15 Bayer US, LLC, Whippany, New Jersey, United States
16 Cardiovascular Clinical Development, Janssen Research and Development, LLC, Raritan, New Jersey, United States
17 Hudson College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States

Address for correspondence: Alex C. Spyropoulos, MD, Department of Medicine, Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, 130 E 77th St, New York, NY 10075, USA (e-mail: aspyropoul@northwell.edu).

Keywords
► aspirin
► combined modality therapy
► hospitalization
► rivaroxaban
► venous thromboembolism

Abstract

Background The MARINER trial evaluated whether postdischarge thromboprophylaxis with rivaroxaban could reduce the primary outcome of symptomatic venous thromboembolism (VTE) or VTE-related death in acutely ill medical patients at risk for VTE. Although aspirin use was not randomized, approximately half of the enrolled patients were receiving aspirin at baseline. We hypothesized that thromboprophylaxis with once-daily rivaroxaban (10 mg or, if creatinine clearance was 30–49 mL/min, 7.5 mg) plus aspirin (R/A) would be superior to placebo without aspirin (no thromboprophylaxis [no TP]).

Methods We compared the primary and major secondary outcomes in the intention-to-treat population in four subgroups defined at baseline: (1) R/A (N = 3,159); (2) rivaroxaban alone (N = 2,848); (3) aspirin alone (N = 3,046); and (4) no TP (N = 2,966). Major bleeding (MB) and nonmajor clinically relevant (NMCR) bleeding were assessed in the safety population on treatment plus 2 days.

Results Patients on R/A had reduced symptomatic VTE and VTE-related death compared with no TP (0.76 vs 1.28%, p = 0.042), and experienced less symptomatic
Introduction

Patients hospitalized with acute medical illness are at increased risk for venous thromboembolism (VTE) during a hospital stay as well as after discharge. While the benefits of inpatient anticoagulant thromboprophylaxis are well established, postdischarge prophylaxis confers a trade-off between reduction in VTE and increased major bleeding (MB). Professional society guidelines recommend thromboprophylaxis in hospitalized, medically ill patients with low-dose unfractionated heparin, low-molecular-weight heparin, or fondaparinux, but do not recommend routine use of postdischarge prophylaxis due to uncertain net clinical benefit. In addition, data suggest that dual pathway inhibition with low-dose anticoagulants plus aspirin is more effective than an anticoagulant alone in reducing major and fatal thromboembolic disease. As such, the addition of aspirin to low-dose rivaroxaban (10 mg once daily) in medically ill patients has shown favorable benefit/risk profiles in trials of extended-duration postdischarge thromboprophylaxis for key medically ill patient subgroups at high risk of VTE and low bleed risk and have been approved by the U.S. Food and Drug Administration to reduce the risk of symptomatic VTE and VTE-related death following hospitalization for an acute medical illness. Low-dose aspirin may be similarly beneficial as postdischarge thromboprophylaxis, in particular, after hip or knee arthroplasty, and has been suggested for use by guidelines. In addition, data suggest that dual pathway inhibition with low-dose anticoagulants plus aspirin is more effective than an anticoagulant alone in reducing major and fatal thromboembolic disease. As such, the addition of aspirin to low-dose rivaroxaban (10 mg once daily) in medically ill patients has the potential to confer additional benefit.

The MARINER trial evaluated whether rivaroxaban given postdischarge reduced symptomatic VTE and VTE-related death among high-risk patients hospitalized with acute medical illness. Rivaroxaban at the doses tested did not achieve a significant reduction in the primary end point of symptomatic VTE or VTE-related death, but did reduce the secondary end point of symptomatic VTE and all-cause mortality (ACM). Although aspirin use was not randomized, more than half of the 12,019 patients in the MARINER trial were prescribed aspirin at baseline. It was therefore of interest to explore whether patients receiving dual pathway inhibition with rivaroxaban and aspirin might be associated with increased benefit compared with those receiving neither agent. For this post hoc analysis, we hypothesized that treatment with rivaroxaban plus aspirin would be superior to use of neither rivaroxaban nor aspirin in preventing major thromboembolic outcomes and death.

Methods

The MARINER trial (NCT02111564) was a multicenter, randomized, double-blind, placebo-controlled, event-driven efficacy and safety study that evaluated rivaroxaban compared with placebo, in the prevention of symptomatic VTE events and VTE-related deaths post–hospital discharge in high-risk medically ill patients. MARINER was conducted at 671 centers in 36 countries from June 2014 through January 2018. Patients were randomized in a 1:1 ratio. Patients with normal renal function consisting of creatinine clearance ≥ 50 mL/min received rivaroxaban 10 mg once daily (or placebo), while those with renal impairment consisting of creatinine clearance 30 to 49 mL/min received rivaroxaban 7.5 mg once daily (or placebo). Treatments were given for a period of 45 days post–hospital discharge. While aspirin use was not randomized, approximately half of the enrolled patients were receiving low-dose aspirin (<162 mg/day) at baseline, while the rest were not on any aspirin.

To be eligible, patients had to be at least 40 years of age and hospitalized for an acute medical condition such as heart failure, acute respiratory insufficiency or acute exacerbation of chronic obstructive pulmonary disease, acute ischemic stroke, acute infectious disease, or inflammatory disease including rheumatic disease for 3 to 10 consecutive days prior to randomization. Patients also needed to be at increased risk of VTE as demonstrated by an International Medical Prevention Registry on VTE (IMPROVE) risk score of 4 or greater (or a risk score of 2 or 3 with plasma D-dimer level ≥ 2× the upper limit of normal during the index hospitalization). Patients with active cancer, active gastrointestinal ulcer or significant bleeding within 3 months, history of hemorrhagic stroke, severe renal insufficiency or liver disease, or bronchiectasis, those who required anticoagulation, strong CYP3A4 inhibitors or inducers, aspirin >162 mg/day, clopidogrel >75 mg/day, or ticlopidine >250 mg twice daily, clopidogrel at any dose in combination with omeprazole or esomeprazole, dipyridamole >400 mg/day, cilostazol >200 mg/day, other P2Y12 receptor antagonists, or
thrombin-receptor antagonists, or those who required dual antiplatelet therapy were excluded from the MARINER trial.

The primary hypothesis of the MARINER trial was that rivaroxaban was superior to placebo for the prevention of the composite outcome of symptomatic VTE (i.e., lower extremity deep vein thrombosis [DVT] or nonfatal pulmonary embolism [PE]) and VTE-related death (i.e., death due to PE or death in which PE could not be ruled out) and was assessed in the intention-to-treat (ITT) population. The results of this trial have been reported previously.6 The hypothesis for this study was that dual antithrombotic therapy (rivaroxaban and low-dose aspirin) would be superior to no antithrombotic therapy.

Secondary efficacy end points assessed in the ITT population included: symptomatic VTE; VTE-related death; symptomatic VTE and ACM; symptomatic VTE/myocardial infarction (MI)/nonhemorrhagic stroke/cardiovascular (CV) death; and ACM. MB and nonmajor clinically relevant (NMCR) bleeding were assessed in the safety population from randomization to 2 days after the last dose of study medication. All end points were adjudicated by a central independent clinical events committee, which was blinded to treatment assignment (Appendix A).

Patients were categorized into one of four subgroups defined at baseline: (1) rivaroxaban alone (10 mg once daily for 45 days with dose reduction to 7.5 mg once daily if baseline creatinine clearance was 30–49 mL/min); (2) aspirin (≤162 mg daily) alone; (3) rivaroxaban plus aspirin (R/A); (4) neither rivaroxaban nor aspirin (no thromboprophylaxis [no TP]). Incidences were compared using chi-square testing, without adjustment for multiplicity. Aspirin use at baseline was not randomized and aspirin use beyond baseline was not investigated, although the protocol allowed aspirin use to continue post–hospital discharge at the discretion of the investigator.

As aspirin use at baseline was not randomized, we also performed a sensitivity analysis, where baseline demographic covariates (shown in Table 1) were tested for significant association with the primary end point using a Cox model with backward variable selection procedure using a cutoff of \( p < 0.05 \) to stay in the model. Those covariates that stayed in the model were then adjusted for in the final Cox proportional hazards model. This approach was also done for the composite end point of symptomatic VTE and ACM as well as for ACM alone.

### Results

The baseline demographic and clinical characteristics of the patients in each subgroup are shown in Table 1. Overall, in groups taking aspirin there were more males, fewer Hispanic or Latino patients, and fewer smokers and patient with a history of cancer, but more patients with renal insufficiency, lower limb paralysis or paresis, and hospitalization for acute ischemic stroke or heart failure.

The results of the primary and major secondary efficacy and safety end points by subgroup are displayed in Table 2. R/A was associated with a significant reduction of the primary efficacy outcome of symptomatic VTE and VTE-related death (0.76 vs 1.28%, \( p = 0.042 \)) compared with no TP. Additionally, the event incidences for rivaroxaban alone (0.91%) or aspirin alone (0.92%) were similar and numerically higher than with combination therapy (0.76%). The combination of rivaroxaban and aspirin was associated with a significant reduction of symptomatic VTE and ACM (1.20 vs 2.12%, \( p = 0.005 \)), as well as ACM alone (1.04 vs 1.82%, \( p = 0.01 \)), compared with no TP. Of note, the aspirin-alone group was also associated with reduced ACM (1.15 vs 1.82%, \( p = 0.03 \)).

As a sensitivity analysis, we adjusted for differences in baseline demographic covariates. The final model included age, D-dimer, and baseline diastolic BP but treatment was no longer significant (\( p = 0.063 \)). However, when an adjusted model was used for symptomatic VTE or ACM, treatment with R/A remained significant compared with no TP (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.40–0.90; \( p = 0.014 \)) as it did in an adjusted model for ACM alone (HR, 0.63; 95% CI, 0.41–0.98; \( p = 0.041 \)).

MB was low in all groups but numerically higher in the groups with rivaroxaban (0.28 and 0.29% with rivaroxaban alone and R/A, respectively), intermediate with aspirin alone (0.20%), and lowest in the no TP group (0.10%), NMCR bleeding was increased with combination therapy compared with no TP (1.49 vs 0.78%, \( p = 0.009 \)).

### Discussion

In this post hoc analysis of the MARINER trial among patients who were at elevated risk of VTE in the immediate postdischarge period, the use of rivaroxaban plus aspirin at baseline was associated with a significant 40% lower risk of symptomatic VTE and VTE-related death, and a significant 52% lower risk of symptomatic VTE and ACM compared with no TP. Patients receiving dual antithrombotic therapy also experienced a 43% lower risk of ACM compared with those receiving no treatment. Moreover, dual antithrombotic therapy showed an advantage over monotherapy with either rivaroxaban or aspirin alone without numerically important increases in MB, despite increased NMCR bleeding.

Previous studies of postdischarge thromboprophylaxis with DOACs have shown significant reductions in VTE among subgroups of patients with specific risk factors, particularly age over 75 years, elevated D-dimer, and IMPROVE score ≥ 16.7,8,15 Additional analyses of DOACs in these cohorts have shown reductions in major and fatal CV events.13,16,17 Substudies of the APEX trial have shown that extended thromboprophylaxis with betrixaban reduces ACM, stroke, and ischemic stroke, particularly among high-risk patients with ischemic stroke or congestive heart failure as the index event,16 as well as fatal or irreversible events, particularly among patients with elevated D-dimer,13 compared with standard prophylaxis. A prespecified MARINER subanalysis showed a 28% reduction in major and fatal thromboembolic events without increased MB among patients randomized to rivaroxaban 10 mg daily compared with placebo.17
|                          | Rivaroxaban alone (N = 2,848) | ASA alone (N = 3,046) | Rivaroxaban + ASA (N = 3,159) | No rivaroxaban + no ASA (N = 2,966) | p-Value |
|--------------------------|-------------------------------|-----------------------|-------------------------------|-------------------------------------|---------|
| Male, %                  | 49.3                          | 54.8                  | 54.6                          | 50.0                                | <0.0001 |
| Race, %                  |                               |                       |                               |                                     |         |
| White                    | 95.8                          | 97.1                  | 96.7                          | 96.1                                | 0.10    |
| Black                    | 1.2                           | 0.7                   | 1.2                           | 1.2                                 |         |
| Asian                    | 0.1                           | 0.1                   | 0.2                           | 0.2                                 |         |
| Other^                   | 3.0                           | 2.1                   | 1.9                           | 2.5                                 |         |
| Ethnicity, %             |                               |                       |                               |                                     |         |
| Hispanic or Latino       | 11.1                          | 6.4                   | 5.8                           | 9.7                                 | <0.0001 |
| Not Hispanic or Latino   | 88.6                          | 93.3                  | 94.0                          | 90.0                                |         |
| Unknown                  | 0.4                           | 0.3                   | 0.2                           | 0.4                                 |         |
| Age (y), mean            | 69.4                          | 69.8                  | 70.0                          | 69.5                                | 0.13    |
| Weight (kg), mean        | 79.2                          | 81.3                  | 82.2                          | 80.0                                | <0.0001 |
| CrCl (mL/min), %         |                               |                       |                               |                                     |         |
| 30 to <50                | 17.0                          | 20.9                  | 19.4                          | 15.6                                | <0.0001 |
| 50 to <80                | 36.9                          | 39.7                  | 41.2                          | 38.7                                |         |
| ≥80                      | 46.0                          | 39.4                  | 39.4                          | 45.7                                |         |
| Height (cm), mean        | 166.3                         | 167.9                 | 167.6                         | 166.7                               | <0.0001 |
| BMI (kg/m²), %           |                               |                       |                               |                                     |         |
| < 25                     | 29.6                          | 24.4                  | 22.9                          | 27.6                                | 0.0002  |
| < 25 to <35              | 56.3                          | 63.2                  | 61.7                          | 57.8                                |         |
| ≥35                      | 14.2                          | 12.4                  | 15.4                          | 14.5                                |         |
| Systolic blood pressure (mm Hg), mean | 128                         | 129                  | 129                           | 128                                | 0.075   |
| Diastolic blood pressure (mm Hg), mean | 76                           | 77                   | 77                            | 77                                  | 0.047   |
| Pulse rate (beats/min), mean | 77                           | 73                    | 73                            | 77                                  | <0.0001 |
| Smoking history, %       |                               |                       |                               |                                     |         |
| Never used               | 52.8                          | 56.1                  | 56.3                          | 53.0                                | <0.0001 |
| Current user             | 18.5                          | 14.8                  | 14.8                          | 18.1                                |         |
| Former user              | 28.7                          | 29.1                  | 29.0                          | 28.9                                |         |
| History of cancer, %     | 8.8                           | 7.8                   | 7.5                           | 9.9                                 | 0.0033  |
| D-dimer, %               |                               |                       |                               |                                     |         |
| >2×ULN                   | 73.6                          | 68.4                  | 67.4                          | 72.7                                | <0.0001 |
| ≤2×ULN                   | 18.8                          | 25.0                  | 26.6                          | 20.2                                |         |
| Not done                 | 7.6                           | 6.6                   | 6.0                           | 7.1                                 |         |
| Duration of hospital stay (mean), d | 6.7                           | 6.8                   | 6.7                           | 6.6                                 | 0.057   |
| Previous VTE, %          | 12.6                          | 11.5                  | 12.9                          | 13.4                                | 0.17    |
| Lower limb paralysis or paresis, % | 13.6                         | 24.7                  | 23.0                          | 12.5                                | <0.0001 |
| Reason for hospitalization, % |                             |                       |                               |                                     |         |
| Acute ischemic stroke    | 8.1                           | 20.7                  | 19.9                          | 7.9                                 | <0.0001 |
| Acute infectious disease | 24.3                          | 10.4                  | 11.3                          | 24.6                                |         |
| Inflammatory disease     | 2.2                           | 0.5                   | 0.7                           | 2.5                                 |         |
| Acute respiratory insufficiency | 37.5                         | 16.9                  | 16.0                          | 37.0                                |         |
| Baseline heart failure   | 27.9                          | 51.5                  | 51.9                          | 28.0                                |         |
The potential advantage of antithrombotic therapy with dual pathway inhibition in reducing major thromboembolism and mortality in our cohort is suggested by results of the COMPASS trial, which showed a 24% relative risk reduction in the composite of stroke, MI, and CV death with low-dose rivaroxaban (2.5 mg twice daily) in combination with low-dose aspirin, compared with low-dose aspirin alone, in individuals with chronic CV disease over a mean follow-up period of 23 months. This regimen in COMPASS suggested reductions in VTE in these patients as well. The increased MB among COMPASS patients receiving long-term dual therapy was, not surprisingly, an order of magnitude higher than in the present study (3.1 vs 0.29%), which evaluated dual therapy only up to 45 days postdischarge. Significantly lower incidences of symptomatic VTE/VTE-related death as well as ACM, with low absolute incidence of MB, suggest a favorable benefit/risk profile for patients who receive dual pathway inhibition with low-dose anticoagulants plus aspirin during the immediate period following acute medical illness.

Since aspirin use was not randomized, comparison of efficacy outcomes can only give an estimate of effectiveness. For example, the incidence of symptomatic VTE or VTE-related death was similar in the rivaroxaban-alone group (0.91%) compared with the aspirin-alone group (0.92%). The comparison of all rivaroxaban versus all placebo, which was randomized, was previously reported (0.83 vs 1.10%). Interestingly, the comparison of all aspirin versus all no aspirin, which was not randomized, yields similar results (0.84 vs 1.10%, respectively), but may certainly be confounded by indication for aspirin use. Nevertheless, the same dose of

### Table 1 (Continued)

| Modified IMPROVE score, % | Rivaroxaban alone (N = 2,848) | ASA alone (N = 3,046) | Rivaroxaban + ASA (N = 3,159) | No rivaroxaban + no ASA (N = 2,966) | p-Value |
|--------------------------|-------------------------------|----------------------|-------------------------------|----------------------------------|---------|
| 2                        | 41.4                          | 29.7                 | 29.1                          | 42.0                             | <0.0001 |
| 3                        | 30.0                          | 31.9                 | 32.7                          | 27.2                             |         |
| 4                        | 28.5                          | 38.4                 | 38.2                          | 30.4                             |         |

Abbreviations: ASA, aspirin; BMI, body mass index; CrCl, creatinine clearance; ITT, intention to treat; ULN, upper limit of normal; VTE, venous thromboembolism.

Note: Chi-square test and one-way analysis of variance test were used for categorical variables and continuous variables, respectively.

"Other includes "American Indian or Alaskan native," "Native Hawaiian or Other Pacific Islander," "Other," "Multiple," and "Unknown" on the case report form.

### Table 2 Effectiveness and safety endpoints in MARINER by treatment group

#### Effectiveness

| End point (up to day 45 in ITT population) | Rivaroxaban alone (N = 2,848) n (%) | ASA alone (N = 3,046) n (%) | Rivaroxaban + ASA (N = 3,159) n (%) | No rivaroxaban + no ASA (N = 2,966) n (%) | p-Value (rivaroxaban + ASA vs no rivaroxaban + no ASA) |
|-------------------------------------------|------------------------------------|----------------------------|------------------------------------|------------------------------------------|---------------------------------------------------|
| Sx VTE + VTE-related death                | 26 (0.91)                          | 28 (0.92)                 | 24 (0.76)                          | 38 (1.28)                                | 0.042                                            |
| VTE-related death                         | 24 (0.84)                          | 18 (0.59)                 | 19 (0.60)                          | 28 (0.94)                                | 0.13                                             |
| Sx VTE                                   | 5 (0.18)                           | 13 (0.43)                 | 6 (0.19)                           | 12 (0.40)                                | 0.12                                             |
| Sx VTE and ACM                           | 40 (1.40)                          | 44 (1.44)                 | 38 (1.20)                          | 63 (2.12)                                | 0.005                                            |
| Sx VTE, MI, nonhemorrhagic stroke and CV death | 44 (1.54)                          | 57 (1.87)                 | 50 (1.58)                          | 63 (2.12)                                | 0.12                                             |
| ACM                                       | 38 (1.33)                          | 35 (1.15)                 | 33 (1.04)                          | 54 (1.82)                                | 0.010                                            |

#### Safety

| End point (on treatment +2 days in safety population) | Rivaroxaban alone (N = 2,833) n (%) | ASA alone (N = 3,032) n (%) | Rivaroxaban + ASA (N = 3,149) n (%) | No rivaroxaban + no ASA (N = 2,948) n (%) | p-Value (rivaroxaban + ASA vs no rivaroxaban + no ASA) |
|------------------------------------------------------|------------------------------------|----------------------------|------------------------------------|------------------------------------------|---------------------------------------------------|
| Major Bleeding                                      | 8 (0.28)                           | 6 (0.20)                   | 9 (0.29)                           | 3 (0.10)                                 | 0.11                                             |
| NMCR Bleeding                                       | 38 (1.34)                          | 38 (0.92)                  | 47 (1.49)                          | 23 (0.78)                                | 0.009                                            |

Abbreviations: ACM, all-cause mortality; ASA, Aspirin; CV, cardiovascular; ITT, intention to treat; MI, myocardial infarction; NMCR, non-major clinically relevant, Sx, symptomatic; VTE, venous thromboembolism.
rivaroxaban (10 mg daily) was compared with low-dose aspirin (81 mg) in a large, randomized study evaluating symptomatic VTE after hip or knee arthroplasty (after an initial 5-day course of rivaroxaban in both groups), and both regimens were found to be similar in preventing symptomatic VTE (0.70 vs 0.64%, respectively).\textsuperscript{3} Our hypothesis for this study was that dual antithrombotic therapy (rivaroxaban and low-dose aspirin) would be superior to no antithrombotic therapy.

In an attempt to adjust to differences in covariates between groups at baseline, a Cox proportional hazards model was created using a backward selection process including treatment (R/A vs no TP). When adjusting for baseline demographic covariates associated with the primary end point, significance was lost for the treatment comparison ($p = 0.063$). However, this was not the case in adjusted models for symptomatic VTE and ACM ($p = 0.014$) or ACM alone ($p = 0.041$). These results support the notion that the combination of rivaroxaban and aspirin may reduce important outcomes compared with no treatment for medically ill patients after discharge.

The present study has several strengths, including the large population of at-risk individuals and central adjudication of outcomes in the original study. Results should be interpreted cautiously, however, as the present analyses were not prespecified, aspirin use at baseline was not randomized, and aspirin use beyond baseline was not recorded. Therefore, only effectiveness can be assessed, and the results may be confounded as aspirin use is clearly higher in certain population (e.g., patients with ischemic stroke and heart failure). The adjusted analyses partially support effectiveness, but not on the primary end point and there was no adjustment for multiplicity. In addition, other confounders could still exist that were not captured in the model. Finally, the number of patients with MB was very small and thus comparisons may be underpowered to detect clinically meaningful differences. Notwithstanding these limitations, this study adds to existing literature suggesting an advantage of dual pathway inhibition as an antithrombotic strategy in reducing major and fatal thrombotic events among cohorts of high-risk medically ill individuals.

**Conclusion**

Extended postdischarge thromboprophylaxis with rivaroxaban in addition to baseline aspirin use was associated with fewer thromboembolic events and a lower rate of VTE-related death compared with lack of either therapy in previously hospitalized medical patients at risk for major thrombotic events in an unadjusted analysis. This observation lost significance after adjustment for differences in covariates at baseline. However, even after adjustment, there were nominally significant reductions in symptomatic VTE and ACM as well as ACM alone. Efficacy results were intermediate and similar in the rivaroxaban-alone or aspirin-alone groups. The incidence of MB was similar among groups, though NMCR bleeding was increased with dual antithrombotic therapy compared with no TP. These findings suggest the need for confirmation in a prospective, randomized trial.

**Essentials**

- A DOAC plus aspirin may reduce postdischarge thrombosis compared with no antithrombotic therapy.
- This post hoc analysis of the MARINER trial compared rivaroxaban, aspirin, both, or neither as postdischarge thromboprophylaxis.
- Dual antithrombotic therapy was associated with fewer VTE events and death than no prophylaxis.
- Considering low absolute bleeding rates, dual antithrombotic prophylaxis merits study in prospective trials.

**Author Contributions**

All authors have contributed equally to the manuscript: (1) conception and design of the work, and analysis and interpretation of the data; (2) drafting the work or revising it critically for important intellectual content including: Introduction, Methods, Results, and 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 questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Funding/Acknowledgments**

Janssen Research & Development LLC sponsored the MARINER study.

**Conflict of Interest**

Alex C. Spyropoulos: Janssen Research & Development LLC, Bayer, Portola, Boehringer Ingelheim, Daiichi Sankyo, ATLAS group; Mark Goldin: Janssen Research & Development LLC; Walter Ageno: Janssen Research & Development LLC, Bayer, Portola, Daiichi Sankyo, Aspen, BMS, Pfizer, Sanofi, Leo Pharma; Gregory W. Albers: Janssen Research & Development LLC, Bayer; C. Greg Elliott: Janssen Research & Development LLC, Bayer; Jonathan L. Halperin: Janssen Research & Development LLC, Abbott, Bayer, Boehringer Ingelheim, National Institute of Health, ATLAS group, Johnson & Johnson, Ortho-McNeil-Janssen; William R. Hiatt: Janssen Research & Development LLC, Bayer, NIH; Gregory Maynard: Janssen Research & Development LLC; P. Gabriel Steg: Janssen Research & Development LLC, Bayer, Merck, Sanofi, Servier, Amarin, Ageno, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Novartis, Regeneron, Lilly, AstraZeneca, Idorsia, Novo-Nordisk; Jeffrey I. Weitz: Janssen Research & Development LLC, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Ionis, Merck, Novartis, Pfizer, Portola, Anthos, Servier; Theodore E. Spiro: Bayer U.S. LLC; Wentao Lu, Janssen Research and Development LLC; Jessica Marigliano, Janssen Research and Development LLC; Gary E. Raskob: Janssen Research & Development LLC, Bayer, BMS, Daiichi Sankyo, Boehringer Ingelheim, Eli Lilly, Pfizer,
Portola, Novartis, Anthos, Tetherex; Eliott S. Barnathan: Janssen Research & Development LLC.

References
1 Hull RD, Merali T, Mills A, Stevenson AL, Liang J. Venous thromboembolism in elderly high-risk medical patients: time course of events and influence of risk factors. Clin Appl Thromb Hemost 2013;19(04):357–362
2 Spyropoulos AC, Anderson FA Jr, FitzGerald G, et al; IMPROVE Investigators. Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest 2011;140(03):706–714
3 Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med 2007;146(04):278–288
4 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
5 Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2, Suppl):e195S–e226S
6 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(22):3198–3225
7 Cohen AT, Harrington RA, Goldhaber SZ, et al; APEX Investigators. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. N Engl J Med 2016;375(06):534–544
8 Spyropoulos AC, Ageno W, Albers GW, et al; MARINER Investigators. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. N Engl J Med 2018;379(12):1118–1127
9 Anderson DR, Dunbar M, Murnaghan J, et al. Aspirin or rivaroxaban for VTE prophylaxis after hip or knee arthroplasty. N Engl J Med 2018;378(08):699–707
10 Anderson DR, Dunbar MJ, Bohm ER, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. Ann Intern Med 2013;158(11):800–806
11 Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377(14):1319–1330
12 Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med 2020;382(21):1994–2004
13 Gibson CM, Korjian S, Chi G, et al; APEX Investigators. 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(07):e006015
14 Tomkowski WZ, Davidson BL. Thromboprophylaxis by rivaroxaban, aspirin, both, or placebo after hospitalization for medical illness. Thromb Res 2019;180:62–63
15 Ageno W, Lopes RD, Goldin M, et al. Rivaroxaban for extended thromboprophylaxis in acutely ill medical patients 75 years of age or older. J Thromb Haemost 2021;19(11):2772–2780
16 Gibson CM, Chi G, Halaby R, et al; APEX Investigators. Extended-duration betrixaban reduces the risk of stroke versus standard-dose enoxaparin among hospitalized medically ill patients: an APEX trial substudy (acute medically ill venous thromboembolism prevention with extended duration betrixaban). Circulation 2017;135(07):648–655
17 Spyropoulos AC, Ageno W, Albers GW, et al. Post-discharge prophylaxis with rivaroxaban reduces fatal and major thromboembolic events in medically ill patients. J Am Coll Cardiol 2020;75(25):3140–3147

Appendix A
Submission of a suspected event for adjudication by the Clinical Events Committee (who was blinded to treatment assignment) was required for:

- All deaths.
- Suspected events that included symptoms or signs suggestive of PE or DVT.
- Performance of any imaging or other diagnostic study that could have yielded an incidental diagnosis of PE or DVT.
- Suspected events that included acute coronary syndrome or myocardial infarction. Chest pain determined not to be cardiac in origin did not need to be sent for adjudication.
- Suspected events that included symptoms compatible with a transient ischemic attack or stroke. Events determined not to be a transient ischemic attack or stroke (e.g., seizure, hypoglycemia) did not need to be sent for adjudication.

Any study outcome event (efficacy or safety) found on autopsy was reported on the appropriate outcome event page in the clinical database.

Any clinical event that suggested the possibility that an efficacy outcome event had occurred (including acute coronary syndrome and transient ischemic attack) was reported on the appropriate case report form page and sent for adjudication. Ultrasound imaging studies from cases of suspected DVT were evaluated. Adjudicated results were used for the final analyses.

All deaths were adjudicated as far as the cause of death by the Clinical Events Committee using all available information, including but not limited to a specific death case report form page, a hospital admission history and physical, a death summary, and an autopsy report.