# The MARINER trial* of rivaroxaban after hospital discharge for medical patients at high risk of VTE

## Design, rationale, and clinical implications

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**Summary**

Hospital-associated venous thromboembolism (VTE) is a leading cause of premature death and disability worldwide. Evidence-based guidelines recommend that anticoagulant thromboprophylaxis be given to hospitalised medical patients at risk of VTE, but suggest against routine use of thromboprophylaxis beyond the hospital stay. The MARINER study is a randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of thromboprophylaxis using rivaroxaban, begun at hospital discharge and continued for 45 days, for preventing symptomatic VTE in high-risk medical patients. Eligible patients are identified using the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE VTE) risk score, combined with a laboratory test, D-dimer. The rivaroxaban regimen is 10 mg once daily for patients with CrCl ≥ 50 ml/min, or 7.5 mg once daily for patients with CrCl ≥ 30 ml/min and < 50 ml/min. The primary efficacy outcome is the composite of symptomatic VTE (lower extremity deep-vein thrombosis and non-fatal pulmonary embolism) and VTE-related death. The principal safety outcome is major bleeding. A blinded clinical events committee adjudicates all suspected outcome events. The sample size is event-driven with an estimated total of 8,000 patients to acquire 161 primary outcome events. Study design features that distinguish MARINER from previous and ongoing thromboprophylaxis trials in medically ill patients are: (i) use of a validated risk assessment model (IMPROVE VTE) and D-dimer determination for identifying eligible patients at high risk of VTE, (ii) randomisation at the time of hospital discharge, (iii) a 45-day treatment period and (iv) restriction of the primary efficacy outcome to symptomatic VTE events.

**Keywords**

Venous thromboembolism, anticoagulants, deep-vein thrombosis, pulmonary embolism, thromboprophylaxis, rivaroxaban, medical patients

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## Introduction

Venous thromboembolism (VTE) is a major contributor to global disease burden (1), and hospital-associated VTE is a leading cause of premature death and disability worldwide (2). Patients hospitalised for acute medical illness are at significant risk of developing VTE, both during their hospital stay and for up to three months after discharge (3–5). In fact, approximately 75 % of all autopsy-documented fatal pulmonary emboli in hospitalised patients occur in the medically ill (6). Using data from the Healthcare Cost and Utilisation (HCUP) project in the United States, Anderson et al. reported that an estimated 8 million hospitalised acutely ill medical patients were at risk of VTE in 2003 (7). A cross-sectional study in 32 countries reported that about 41 % of all hospitalised medical patients have a sufficiently high risk of VTE to warrant thromboprophylaxis (8).

Evidence-based guidelines recommend that anticoagulant thromboprophylaxis be given to hospitalised medical patients at increased risk of VTE (9, 10), and that prophylaxis should be given for 6-21 days until the patient is fully mobile or is discharged from hospital, whichever comes first (9). The guidelines suggest against the routine use of extended thromboprophylaxis beyond the acute

 

hospital stay (9). This latter recommendation is based on the results of clinical trials (11–13) that failed to establish a definitive net clinical benefit of extended thromboprophylaxis with low-molecular-weight heparin or direct-acting oral anticoagulants (DOACs). In these earlier studies, increased rates of major bleeding offset the benefits of reduced VTE (11, 13) or efficacy was not demonstrated (12). Recent cohort studies indicate that the risk of symptomatic VTE in subgroups of medically ill patients ranges from 1.9% to 3.8% during the 90 days after hospital discharge (5, 14). Optimising the benefit-to-risk profile of extended thromboprophylaxis for such patients remains an important unmet need (15). Improved patient selection, both by identifying those at high risk of VTE, and by excluding those at high risk of bleeding, is key to resolving this unmet need (15).

The MARINER study is a randomised, double-blind trial to evaluate the efficacy and safety of thromboprophylaxis using rivaroxaban given after hospital discharge for preventing symptomatic VTE in high-risk medical patients (ClinicalTrials.gov Identifier: NCT02111564). This trial uses the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE VTE) risk score, an evidence-derived and validated risk assessment model for VTE (4, 16, 17), combined with D-dimer, a readily available laboratory test (18, 19), to identify patients with a sufficiently high risk of VTE to justify the risk of bleeding associated with extended anticoagulant prophylaxis. The study design also uses strategies to reduce the risk of bleeding observed in prior thromboprophylaxis studies in medically ill patients (11–13). The goals of this article are to a) summarise the rationale and design of the MARINER trial, b) describe the unique design features of the study and c) discuss the potential implications for clinical practice.

# Methods

## Study objectives and hypothesis

The primary objective is to assess the efficacy and safety of rivaroxaban compared with placebo for the prevention of symptomatic VTE and VTE-related death post-hospital discharge in medically ill patients at high risk for VTE. The primary hypothesis is that rivaroxaban will be superior to placebo for the prevention of the composite outcome of symptomatic non-fatal VTE and VTE-related death. The key secondary objective is to test the hypothesis that rivaroxaban will be superior to placebo for reducing VTE-related death. Other secondary and additional objectives are listed in ►Table 1.

## Study design

### Overview and study oversight

MARINER is a multinational, multicentre, randomised, double-blind, placebo-controlled, parallel group trial. The study consists of a screening phase, a 45-day double-blind treatment phase beginning at the time of hospital discharge and a 30-day safety follow-up period (►Figure 1). The sample size is event-driven with an estimated total of approximately 8,000 patients to acquire 161 primary events (see Sample Size and Statistical Analysis).

The study is coordinated by an Executive Committee (EC) composed of members of the academic leadership of the study and two members from the sponsor. An Independent Data Monitoring Committee (IDMC) monitors patient safety and outcomes at intervals during the study and makes recommendations to the EC regarding ongoing trial conduct. A Clinical Events Committee (CEC), whose members are unaware of treatment allocation,

**Table 1: Objectives of the MARINER Trial.**

| |
|---|
| **Primary objective** |
| • To assess the efficacy and safety of rivaroxaban compared with placebo for the prevention of symptomatic VTE and VTE-related death post-hospital discharge in high-risk, medically ill patients |
| **Secondary objectives** |
| • To compare rivaroxaban with placebo in the following post-discharge outcomes: |
| – VTE-related death (death due to PE or death in which PE cannot be ruled out) |
| – Symptomatic non-fatal VTE (lower extremity DVT or PE) |
| – Composite of symptomatic non-fatal VTE and all-cause mortality |
| – Composite of symptomatic non-fatal VTE, myocardial infarction, non-haemorrhagic stroke and cardiovascular death (death due to a known cardiovascular cause and death in which a cardiovascular cause, including PE, cannot be ruled out) |
| – All-cause mortality |
| **Exploratory objectives** |
| • To compare rivaroxaban with placebo in the following post-discharge outcomes: |
| – Symptomatic lower extremity DVT |
| – Symptomatic non-fatal PE |
| – Symptomatic upper extremity DVT |
| – Myocardial infarction |
| – Non-haemorrhagic stroke |
| – Rehospitalisation for symptomatic VTE within 30 days after randomisation |
| **Pharmacokinetic objectives** |
| • To assess the kinetics of rivaroxaban |
| • To describe drug exposure based on CrCl |
| **Medical resource utilisation and health economics objective** |
| • To assess the following cost drivers |
| – Rehospitalisation (including emergency room visits and intensive care unit and cardiac care unit stays) |
| – Length of stay and subject discharge destination (after rehospitalisation) |

CrCl, creatinine clearance; DVT, deep-vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

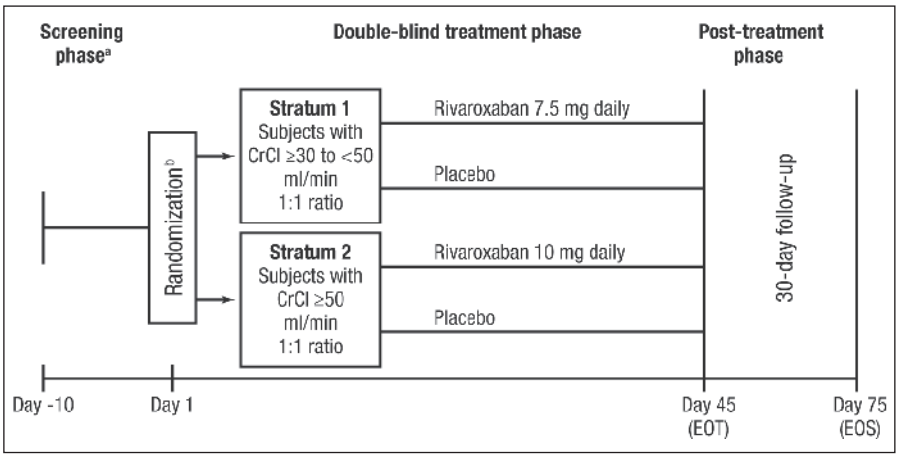


**Figure 1: Study design.** EOT, end of treatment; EOS, end of study. [a]3–10 days of hospitalisation. [b]Done on the day or day after the patient leaves the hospital.

adjudicates all suspected episodes of VTE, bleeding, myocardial infarction, stroke and all deaths, using criteria defined a priori. The protocol was reviewed by regulatory authorities and by institutional review boards or ethics committees at each centre. Informed consent is obtained from eligible patients prior to study-related procedures and/or randomisation.

## Patient population and eligibility

The patient population comprises men and women ages 40 years and older who have been hospitalised for the new onset or exacerbation of one of the following conditions: heart failure with a left ventricular ejection fraction ≤45%, acute respiratory insufficiency or acute exacerbation of chronic obstructive pulmonary disease, acute ischaemic stroke (including spinal cord infarction if there is no evidence of intramedullary, subdural or epidural haemorrhage), or acute infectious or acute inflammatory disease, including rheumatic diseases.

**Table 2: Modified IMPROVE VTE Risk Score.**

| VTE Risk Factor | VTE Risk Score |
|---|---|
| Previous VTE | 3 |
| Known thrombophilia[a] | 2 |
| Current lower limb paralysis or paresis[b] | 2 |
| History of cancer[c] | 2 |
| ICU/CCU stay | 1 |
| Complete immobilisation[d] ≥1 day | 1 |
| Age ≥60 years | 1 |

CCU, cardiac care unit; ICU, intensive care unit; NIH, National Institutes of Health; VTE, venous thromboembolism. [a]A congenital or acquired condition leading to excess risk of thrombosis (e.g. factor V Leiden, lupus anticoagulant, factor C or factor S deficiency). [b]Leg falls to bed by 5 seconds, but has some effort against gravity (taken from NIH stroke scale). [c]Cancer (excluding non-melanoma skin cancer) present at any time in the last 5 years (cancer must be in remission to meet eligibility criteria). [d]Confined to bed or chair with or without bathroom privileges.

The index hospitalisation must be at least three and no more than 10 consecutive days in duration. Eligible patients must have an increased VTE risk, as demonstrated by a total modified IMPROVE VTE risk score (4, 16, 17) ≥4, or a risk score of 2 or 3 and a plasma D-dimer level more than twice the upper limit of normal. The modified IMPROVE VTE risk score is shown in ▶Table 2. The plasma D-dimer level is measured locally using a blood sample collected after the start of the index hospitalisation and before randomisation; the value obtained closest to the beginning of the index hospitalisation is used. Eligible patients must also have received thromboprophylaxis during the index hospitalisation with low-molecular-weight heparin or unfractionated heparin (fondaparinux is not permitted).

Patients who have a medical condition (e.g. atrial fibrillation) that requires administration of any parenteral or oral anticoagulant during the study are not eligible for participation. In addition, patients with a history of recent (within three months) bleeding or who are at particularly high risk of bleeding because of concomitant conditions, drugs or procedures, and those with other contraindications to rivaroxaban will be excluded. The full list of exclusion criteria is provided in ▶Table 3.

## Randomisation and stratification

Patients who meet all of the inclusion and none of the exclusion criteria will be randomly assigned to receive rivaroxaban or placebo in a 1:1 ratio. Randomisation is to occur on the same day as, or the day after the patient leaves the hospital, and may occur at the hospital, clinic or other discharge destination. The day of randomisation is Day 1 of the study. At the randomisation visit, patients and family members, as appropriate, will be counselled and given educational material on the symptoms and signs associated with deep-vein thrombosis, pulmonary embolism and bleeding, and instructed to promptly report any such symptoms or signs.

Central randomisation will be used and patients will be randomly assigned to the rivaroxaban or placebo treatment groups based on a computer-generated randomisation schedule prepared before the study. The randomisation will be balanced by using randomly permuted blocks of four and will be stratified by country

and by whether the creatinine clearance (CrCl) is ≥ 30 and < 50 ml/minute (min) or is ≥ 50 ml/min, measured during the two days before hospital discharge or later, but before randomisation. Enrollment may be capped for subgroups with certain baseline characteristics (e.g. index hospitalisation duration, reason for index hospitalisation, VTE risk score and index hospitalisation thromboprophylaxis) or by country or region.

## Rivaroxaban regimen and rationale

The rivaroxaban regimen is 10 mg once daily in patients with CrCl ≥ 50 ml/min, or a reduced once-daily dose of 7.5 mg for patients with moderate renal impairment (CrCl ≥ 30 and < 50 ml/min). This approach is based on the results of a previous trial, MAGELLAN (13), which demonstrated that although extended prophylaxis with a 10-mg, once-daily dose of rivaroxaban reduced the risk of VTE, this benefit was offset by increased bleeding. The increase in bleeding was particularly evident in patients with moderate renal impairment. In the ROCKET AF study (20), a 25 % dose reduction of rivaroxaban (from 20 mg to15 mg once daily) was used in patients whose CrCl was 30 to 49 ml/min. This dose reduction provided drug exposure, efficacy and safety comparable to that of rivaroxaban 20 mg once daily, which was the dose administered to patients with CrCl ≥ 50 ml/min (21, 22). Based on population pharmacokinetic simulations in a medically ill population, a 25 % reduction in the dose of rivaroxaban from 10 mg to 7.5 mg daily in patients with CrCl of 30 to 49 ml/min is predicted to yield rivaroxaban plasma exposures similar to those in patients with CrCl ≥ 50 ml/min who are given the 10-mg dose (22).

The first dose of study drug is to be given no later than the day after the patient leaves the hospital and as soon after randomisation as possible. Study drug is taken with or without food and is continued for 45 days. This duration was chosen because follow-up studies of medical patients at high risk of VTE have found that

**Table 3: Exclusion criteria.**

| | |
|---|---|
| **Bleeding Risk-related Criteria** | |
| 1 | Any bleeding (defined as bleeding requiring hospitalisation, transfusion, surgical intervention, invasive procedures, occurring in a critical anatomical site or causing disability) within 3 months prior to randomisation or occurring during index hospitalisation. |
| 2 | Major surgery, biopsy of a parenchymal organ, ophthalmic surgery (excluding cataract surgery) or serious trauma (including head trauma) within 4 weeks before randomisation. |
| 3 | Any planned major surgery (see exclusion criterion #2) or major invasive diagnostic procedure intended during the duration of the trial. |
| 4 | Subjects with any known coagulopathy or bleeding diathesis, or an INR > 1.5 during the index hospitalisation without a subsequent value (the last value before randomisation) that is ≤ 1.5. |
| 5 | A history of haemorrhagic stroke or any intracranial bleeding at any time in the past, evidence of primary intracranial haemorrhage on CT or magnetic resonance imaging scan of the brain, or clinical presentation consistent with intracranial haemorrhage. This applies as well to subjects hospitalised for ischaemic stroke upon randomisation. |
| 7 | Subject has a history of or current intracranial neoplasm (benign or malignant), cerebral metastases, AV malformation or aneurysm. |
| 8 | Active gastroduodenal ulcer, defined as diagnosed within 3 months or currently symptomatic or known AV malformations of the gastrointestinal tract. |
| 9 | Screening platelet count < $75 \times 10^9$ cells/l. |
| **Concomitant Conditions or Diseases** | |
| 10 | Active cancer (excluding non-melanoma skin cancer) defined as cancer not in remission or requiring active chemotherapy or adjunctive therapies, such as immunotherapy or radiotherapy. Chronic hormonal therapy (e.g. tamoxifen, anastrazole, leuprolide acetate) for cancer in remission is allowed. |
| 11 | Any medical condition (e.g. atrial fibrillation) that requires use of any parenteral or oral anticoagulant(s) (e.g. warfarin sodium or vitamin K antagonists, factor II or Xa inhibitors, fibrinolytics) concomitantly with study medication. |
| 12 | Bilateral and unilateral above-knee lower extremity amputation. |
| 13 | Subject has known allergies, hypersensitivity or intolerance to rivaroxaban or any of its excipients. |
| 14 | Severe renal insufficiency (baseline CrCl < 30 ml/min calculated using the Cockcroft-Gault formula. |
| 15 | Known significant liver disease (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) that is associated with coagulopathy or moderate or severe hepatic impairment. |
| 16 | Known HIV infection. |
| 17 | Sustained uncontrolled systolic BP of ≥ 180 mmHg or diastolic BP of ≥ 100 mmHg at randomisation despite treatment. |
| 18 | Current drug or alcohol abuse, based on investigator's assessment. |
| 19 | Cardiogenic or septic shock with the need for vasopressor(s) or devices for blood pressure support during index hospitalisation. |
| 20 | Presence of inferior vena caval filter. |
| 21 | Severe bronchiectasis or cavitary tuberculosis or any other pulmonary condition (e.g. vasculitis) at risk for major haemoptysis. |

 

**Table 3: Continued**

| Drugs or Procedures | |
|---|---|
| 22 | a.Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin or protease inhibitors) use within 4 days before randomisation, or planned use during the study. Itraconazole use is prohibited within 7 days before randomisation and during the study.<br>b.Combined P-gp and strong CYP3A4 inducers (such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine or St. John's Wort) use within 2 weeks before randomisation, or planned use during the study. |
| 23 | Received fibrinolysis during index hospitalisation, unless received for ischaemic stroke at least 3 full days before randomisation. |
| 24 | Use of antiplatelet therapy during the index hospitalisation, including:<br>a.ASA >162 mg/day.<br>b.Clopidogrel >75 mg/day or ticlopidine >250 mg twice daily.<br>c.Clopidogrel at any dose in combination with omeprazole or esomeprazole<br>d.Dipyridamole >400 mg/day.<br>e.Cilostazol >200 mg/day.<br>f.Dual therapy with 2 or more antiplatelet agents (dipyridamole with ASA is permitted).<br>g.Other G protein–coupled purinergic receptor P2Y (P2Y12) antagonists (e.g. prasugrel, ticagrelor).<br>h.Thrombin-receptor antagonists (e.g. vorapaxar). |
| 25 | Childbearing potential without proper contraceptive measures, pregnancy or breast feeding. |
| 26 | Participation in another pharmacotherapeutic study or with an experimental medical device within 30 days before the start of study treatment. |
| 28 | Prescribed daily use of NSAIDs during the index hospitalisation. |

ASA, acetylsalicylic acid; AV, arteriovenous; BP, blood pressure; CrCl, creatinine clearance; CT, computed tomography; HIV, human immunodeficiency virus; INR, international normalised ratio; NSAID, non-steroidal anti-inflammatory drug.

approximately 75% of the post-hospital VTE events occur by this time (4, 5).

The study drug may be temporarily interrupted for invasive procedures or as medically needed. If a patient is hospitalised for any reason other than symptomatic VTE or bleeding, the study drug is to be continued during the hospitalisation unless the treating physician judges that anticoagulation is clinically indicated. If temporary anticoagulation is indicated, for example, for VTE prophylaxis during the hospital stay, the study drug is to be interrupted temporarily and can be restarted upon discharge at the discretion of the study investigator.

## Efficacy outcomes

The primary efficacy outcome is the composite of all adjudicated confirmed symptomatic VTE events (lower extremity deep-vein thrombosis and non-fatal pulmonary embolism) and VTE-related death (death adjudicated as either due to pulmonary embolism or death in which pulmonary embolism cannot be ruled out as the cause).

The secondary efficacy outcomes in hierarchical order are (i) VTE-related death; (ii) symptomatic VTE; (iii) the composite of symptomatic VTE and all-cause mortality; (iv) the composite of symptomatic VTE, myocardial infarction, non-haemorrhagic stroke and cardiovascular death (death due to a known cardiovascular cause and death in which a cardiovascular cause, including pulmonary embolism, cannot be ruled out); and (v) all-cause mortality.

The exploratory efficacy outcomes include the components of the composite primary efficacy outcome and re-hospitalisation for symptomatic VTE within 30 days after randomisation.

## Safety outcomes

The principal safety outcome is major bleeding using validated ISTH bleeding criteria (23). Other safety outcomes are non-major clinically relevant bleeding and other bleeding.

A major bleeding event is defined as overt bleeding associated with: a decrease in haemoglobin of 2 g/dl or more, or leading to transfusion of two or more units of packed red blood cells or whole blood, or bleeding that occurs in a critical site (e.g. intracranial, intra-spinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal) or fatal bleeding.

Non-major clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding, but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment or associated with discomfort for the subject, such as pain or impairment of activities of daily life. Other bleeding is defined as any other overt bleeding that does not meet the criteria for major or non-major clinically relevant bleeding.

## Assessment of outcomes and follow-up

All patients will have contacts at Day 7 (–2/+5 days) and at Day 21 (–3/+7 days) after randomisation, and all patients, including those who may have discontinued study drug, are to have contact at the end of the treatment period (Day 45, 0/+4 days). The Day 7 contact may be conducted at the clinic or other discharge destination, including a home visit, or as a telephone visit. The Day 21 and Day 45 contacts are to be in person at the clinic or other discharge destination.

At each contact, a clinical status review for suspected outcome events and a symptom assessment, consisting of a set of scripted questions, will be completed. The education and counselling about the symptoms and signs of deep-vein thrombosis, pulmonary embolism and bleeding will be repeated, and data on adverse events and concomitant medications will be collected.

All patients are to be contacted for safety follow-up 30 days after discontinuing study drug (Day 75, end of study –5/+5 days).

## Sample size and statistical analysis

The study sample size is event-driven using a time-to-event analysis. The targeted total number of primary efficacy outcome events is 161. If a subject has multiple events, only the first is counted toward study size determination. The targeted total number of events was determined assuming a 40% relative risk reduction in the primary efficacy outcome with rivaroxaban, a power of 90%, and a two-sided significance level of 0.05. To observe the targeted 161 events, an estimated total of approximately 8,000 subjects will need to be randomised based on an estimated placebo incidence rate of the primary efficacy outcome of 2.5%. Randomisation may be stopped at approximately 9,000 subjects for administrative considerations even if the targeted 161 events have not been observed. The total number of VTE-related death events may also be taken into account when deciding to stop study enrollment.

An interim analysis for futility will be conducted when approximately 80 adjudicated primary events have occurred (about 50% of the targeted total number of events).

**Table 4: Study design features of randomised trials of extended thromboprophylaxis in medical patients.**

| | EXCLAIM (11) | ADOPT (12) | MAGELLAN (13) | APEX (25) | MARINER |
|---|---|---|---|---|---|
| Drug | Enoxaparin | Apixaban | Rivaroxaban | Betrixaban | Rivaroxaban |
| Regimen | 40 mg once daily | 2.5 mg twice daily | 10 mg once daily | 80 mg once daily | 10 mg once daily |
| Reduced dose in selected patients | No | No | No | Yes[a] | Yes[b] |
| Timing of randomisation | In hospital | In hospital | In hospital | In hospital | At hospital discharge |
| RAM used for patient eligibility | No | No | No | No | Yes |
| D-dimer for patient eligibility | No | No | No | Yes | Yes |
| Treatment duration | 28 ± 4 days after an initial 10 ± 4 days | 30 days | 35 ± 4 days | 35 to 42 days | 45 days |
| Comparator | Placebo | Enoxaparin for at least 6 days | Enoxaparin for 10 ± 4 days | Enoxaparin for 6 to 14 days | Placebo |
| Double-blind design | Yes | Yes | Yes | Yes | Yes |
| Primary efficacy outcome | Asymptomatic proximal DVT and symptomatic VTE through Day 28 Enoxaparin 2.5% Placebo 4% | Asymptomatic proximal DVT and symptomatic VTE through Day 30 Apixaban 2.7% Enoxaparin/placebo 3.1% | Asymptomatic proximal DVT and symptomatic VTE at Days 10 and 35 Rivaroxaban 4.4% on Day 35 Enoxaparin/placebo 5.7% on Day 35 | Asymptomatic proximal DVT and symptomatic VTE through Day 35 | Symptomatic VTE through Day 45 |
| Principal safety outcome | Major bleeding Enoxaparin 0.8% Placebo 0.3% | Bleeding Apixaban 0.5% major 2.7% CRNM Enoxaparin/placebo 0.2% major 2.1% CRNM | Major or CRNM bleeding Rivaroxaban 4.1% on Day 35 Enoxaparin/placebo 1.7% on Day 35 | Major bleeding | Major bleeding |
| Sample size | 5,963 | 6,758 | 8,101 | 6,850 | Event driven 8 to 9,000 |

CrCl, creatinine clearance; CRNM, clinically relevant non-major; DVT, deep-vein thrombosis; RAM, risk assessment model; VTE, venous thromboembolism. [a]Betrixaban 2 doses of 80 mg given on Day 1. Patients with CrCl ≥15 and <30 ml/min or, if taking strong P-gp inhibitor drugs, receive one dose of 80 mg on Day 1 and 40 mg once daily thereafter. [b]Rivaroxaban 7.5 mg if CrCl ≥30 and <50 ml/min.

 

The study analysis will be performed using the intent-to-treat population (all randomised patients who have signed an informed consent) and will include all data and outcomes from randomisation through Day 45 inclusive (end of treatment). The primary efficacy outcome will be analysed based on time from randomisation to the first occurrence of symptomatic VTE or VTE-related death. The hypothesis that rivaroxaban is superior to placebo will be tested using a Cox proportional hazards model, stratified by subjects with CrCl ≥ 30 and < 50 ml/min versus subjects with CrCl ≥ 50 ml/min, with the treatment (as randomised) as the only covariate.

The cumulative event rate derived from the Kaplan-Meier estimate will be displayed graphically to evaluate the treatment effect over time. Homogeneity of treatment effects, both in hazard ratio and direction, will be assessed by subgroups and their interactions with treatment.

Each secondary efficacy outcome will be analysed using the same stratified Cox proportional hazards model as for the primary efficacy outcome. To control the family-wise type I error rate at alpha of 0.05 (2-sided), if superiority of rivaroxaban over placebo on the primary efficacy outcome is established, superiority of rivaroxaban over placebo on secondary outcomes will be tested sequentially using a closed testing procedure in the following hierarchical order, each at alpha of 0.05 (two-sided): (i) VTE-related death; (ii) symptomatic VTE; (iii) the composite of symptomatic VTE and all-cause mortality; (iv) the composite of symptomatic VTE, myocardial infarction, non-haemorrhagic stroke, and cardiovascular death and (v) all-cause mortality.

The bleeding outcomes will be analysed based on time from randomisation to the first occurrence of major bleeding, using the same Cox proportional hazards model as that for the primary efficacy outcome described previously. The analysis will be based on the safety analysis set, according to study drug received, and will use the "on-treatment" analysis phase, defined as the time from randomisation up to and inclusive of two days after the last dose of study drug.

The benefit-risk of rivaroxaban versus placebo will be evaluated based on the excess number of events between treatments for events intended to be prevented (benefits) and events that may be caused (risks). The excess number of events is defined as the difference in efficacy and safety events multiplied by a hypothetical population size (e.g. 10,000 patients). Several analytic approaches will be used. One analysis will use a composite of the primary efficacy outcome (symptomatic VTE or VTE-related death) and the principal safety outcome (major bleeding). A bivariate approach (24) to benefit-risk assessment will also be performed.

## Discussion

Optimising the benefit-to-risk profile of thromboprophylaxis after hospital discharge is an important unmet need for medically ill patients. In addressing this need, the MARINER trial uses unique study design features compared with previous (11–13) and ongoing (25) clinical trials of extended thromboprophylaxis in medical patients (see ▶Table 4).

There are four key unique features of the MARINER study design. First, is the use of an evidence-derived and validated risk assessment model, the IMPROVE VTE risk score (4, 16, 17), for selection of eligible patients. This clinical model, combined with the results of a simple and readily available laboratory test, the plasma D-dimer level, will identify patients who are at high risk of VTE and likely to derive the most benefit from extended thromboprophylaxis. This patient selection process should be generalisable and readily translated to clinical practice.

A second design feature that distinguishes MARINER from previous and ongoing trials of DOACs in medically ill patients (12, 13, 25) is randomisation at the time of hospital discharge when inpatient anticoagulant prophylaxis is completed. With an average length of stay of less than five days for hospitalised medical patients in the United States (26), and global trends also indicating reduced length of stay (27), the burden of VTE in hospitalised medical patients is shifting to the outpatient setting. However, currently less than 4% of patients receive thromboprophylaxis after hospital discharge (14). The timing of randomisation at discharge, rather than at or around the time of admission to hospital, more directly aligns with the clinical question of interest, namely, the benefit-to-risk of prescribing extended thromboprophylaxis. Further, by randomising patients at the completion of inpatient anticoagulant prophylaxis, those patients who are at high risk of having a bleeding complication are most likely to do so during their hospitalisation, and will not enter the trial. By "filtering" out the patients who have bleeding in hospital, a more clinically relevant estimate of the benefit-risk of post-discharge thromboprophylaxis will be obtained because, in practice, bleeding during the hospital stay would usually be a contraindication to continued anticoagulant prophylaxis. Deferring the randomisation to the time of hospital discharge makes sense because the practical advantages of the DOACs over parenteral anticoagulants are most relevant to the outpatient phase of prophylaxis.

In addition to randomisation at the time of hospital discharge, there are other trial design features that are aimed at reducing the risk of bleeding. These include the use of a lower dose of rivaroxaban of 7.5 mg daily in patients with moderate renal impairment and exclusion of patients with active cancer and those taking dual antiplatelet therapy. These design features were prompted by the results of subgroup analyses of the MAGELLAN study (13), which suggested increased major bleeding in these groups of patients. Our hypothesis is that these study design features, taken together, will reduce the risk of major bleeding that was seen in previous trials of extended thromboprophylaxis in the medically ill, and result in an acceptable incidence of major bleeding relative to the benefit obtained for preventing symptomatic VTE.

Third, compared with previous and ongoing studies of extended thromboprophylaxis that used a 30- to 35-day treatment period, the MARINER trial uses a 45-day treatment period. This longer treatment period was selected because recent epidemiological data indicate a continued risk of VTE beyond 30 days (4, 5). Therefore, extending thromboprophylaxis until Day 45 may provide additional benefit.

Fourth, only symptomatic VTE events are included in the primary efficacy outcome in the MARINER trial. Routine case-finding of asymptomatic deep-vein thrombosis with protocol-mandated ultrasonography is not used because the clinical relevance of these events is uncertain. By focusing on symptomatic VTE, the MARINER trial will provide a more clinically relevant assessment of the potential benefit of extended thromboprophylaxis in medical patients, because the reductions in symptomatic VTE appear to be more robust than those in asymptomatic ultrasound-detected VTE events (11–13), and because case-finding with ultrasonography is not routine clinical practice. Our decision to include only symptomatic VTE events in the primary efficacy outcome (which includes VTE-related death) is consistent with the recommendations of recent evidence-based practice guidelines (9). The focus on symptomatic VTE events also provides for a more clinically relevant outcome to offset major bleeding in the benefit-to-risk assessment, since the clinical importance of asymptomatic deep-vein thrombosis detected by screening ultrasonography has been questioned (9). The inclusion of asymptomatic thrombosis in the primary efficacy outcome of previous trials of extended thromboprophylaxis in the medically ill was likely a contributing factor to the conclusion of the uncertain benefit-risk of extended prophylaxis for this patient population.

VTE-related death is a component of the composite primary efficacy endpoint, and will also be evaluated independently as one of a limited number of pre-specified secondary outcomes. Although a recent study using hospital claims data suggests that extended anticoagulant prophylaxis in hospitalised medical patients is associated with reduced mortality within 90 days of discharge (28), definitive evidence of a mortality benefit of post-discharge thromboprophylaxis is lacking. The analysis of VTE-related death is important because prevention of death from VTE is the principal reason for using primary prophylaxis with anticoagulants, rather than clinical surveillance or case-finding with ultrasonography, since the initial presentation of VTE is often sudden or unexpected death. This is especially important in medical patients who have serious heart or lung disease with limited cardiorespiratory reserve, where even a relatively small pulmonary embolism may be fatal. In the MAGELLAN study (13), VTE-related death accounted for approximately 50 % of the total symptomatic VTE events in the placebo group during the extended prophylaxis phase. This is also likely to be the case in the MARINER trial because we are targeting patients at highest risk of VTE. The MARINER design uses an event driven approach for the study sample size, and we have pre-specified that the total number of VTE-related death events may also be taken into account in the decision to end study enrollment. This strategy will provide an opportunity to detect a statistically significant effect on the outcome of VTE-related death, if the rivaroxaban regimen is effective in preventing fatal VTE events. Such a result, if it occurs, would have major implications for clinical practice since the risk of major bleeding is likely to be more acceptable if clinicians and patients have firm evidence of a benefit for preventing fatal VTE. In addition, we will perform an exploratory analysis of our efficacy and safety endpoints utilising a bivariate approach to assess the trade-offs of the primary efficacy and safety outcomes of the trial simultaneously in a non-linear fashion.

In conclusion, the MARINER trial includes unique study design features based on the results and lessons learned from previous clinical trials in hospitalised medical patients with the goal of optimising the benefit-risk profile of extended thromboprophylaxis. Since the majority of fatal VTE events occur in medical patients, if the study hypotheses are correct, the MARINER results may provide a potentially important advance in reducing the global burden of death and disability from VTE.

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**Conflicts of interest**

W. Ageno has served on advisory boards for Bayer Healthcare, Boehringer Ingelheim, BMS-Pfizer, and Daiichi-Sankyo, and has received Travel or research support from Bayer Healthcare, GSK, BMS-Pfizer, Daiichi-Sankyo, and Boehringer Ingelheim. G. W. Albers is a consultant to Johnson & Johnson. G. C. Elliott is employed by Intermountain Healthcare Inc, and has served as a consultant and received honoraria from Janssen, and Bayer. J. L. Halperin has received consulting fees from Ortho-McNeil-Janssen, and Boehringer Ingelheim. L. Haskell is an employee of Janssen Pharmaceuticals, and holds stock in Johnson & Johnson. W. R. Hiatt has received grant support from Bayer, Janssen, AstraZeneca, and GSK. G. A. Maynard serves on the Executive Committee of the MARINER Trial sponsored by Johnson & Johnson. G. Peters is an employee of Johnson & Johnson. G. E. Raskob has served as a paid consultant for Janssen, Bayer, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer, Portola, and Eli Lilly. T. E. Spiro is an employee of Bayer Healthcare Pharmaceuticals Inc. A. C. Spyropoulos has served as a consultant for Janssen, Boehringer Ingelheim, Daiichi-Sankyo, BMS, Pfizer, and the ATLAS group. G. Steg has received research grants from Sanofi, and Servier; speaking or consulting fees from Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, CSL Behring, Daiichi-Sankyo, GSK, Janssen, Lilly, Novartis, Pfizer, Regeneron, Roche, Sanofi, Servier, The Medicines Company; and owns stock from Aterovax. E-Y. Suh is an employee of Janssen R&D LLC. J. Weitz has served as a consultant and has received honoraria from Janssen, Bayer, Johnson & Johnson, BMS, Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Portola. J. Zrubeck is an employee of Janssen Pharmaceuticals.

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