

ORIGINAL RESEARCH

Benefit–Risk of Rivaroxaban for Extended Thromboprophylaxis After Hospitalization for Medical Illness: Pooled Analysis From MAGELLAN and MARINER

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BACKGROUND: Thromboprophylaxis extended after hospital discharge in medically ill patients currently is not recommended by practice guidelines because of uncertainty about the benefit for preventing major or fatal thromboembolic events, and the risk of bleeding.

METHODS AND RESULTS: We assessed the benefit and risk of thromboprophylaxis with rivaroxaban 10 mg once daily extended for 25 to 45 days after hospitalization for preventing major thromboembolism in medically ill patients using the pooled data in 16 496 patients from 2 randomized trials, MARINER (Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolic Risk) and MAGELLAN (Multicenter, randomized, parallel-group efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically ill patients comparing rivaroxaban with enoxaparin). The data from the MARINER trial were pooled with the data from the MAGELLAN trial in patients who were free of thrombotic or bleeding events up to the last dose of enoxaparin/placebo and who continued in the outpatient phase of thromboprophylaxis. The composite outcome of major thromboembolic events (symptomatic deep vein thrombosis, nonfatal pulmonary embolism, myocardial infarction, and nonhemorrhagic stroke) and all-cause mortality was used to assess benefit and was compared with the risk of the composite of fatal and critical site bleeding. The incidence of the composite efficacy outcome was 1.80% (148 of 8222 patients) in the rivaroxaban group, compared with 2.31% (191 of 8274 patients in the placebo group) (HR, 0.78 [95% CI, 0.63–0.97], $P=0.024$). Fatal or critical site bleeding events were infrequent and occurred in <0.1% of patients in both groups (rivaroxaban 0.09%; placebo 0.04%; HR, 2.36; $P=0.214$).

CONCLUSIONS: The results suggest a benefit for reducing major thromboembolic outcomes (number needed to treat: 197), with a favorable trade-off to fatal or critical site bleeding (number needed to harm: 2045).

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifiers: NCT00571649 and NCT02111564.

Key Words: anticoagulants ■ bleeding ■ rivaroxaban ■ thromboembolism ■ thromboprophylaxis

Patients who are hospitalized for acute medical illness are at increased risk for venous thromboembolism.¹ Anticoagulant thromboprophylaxis reduces the risk of in-hospital venous thromboembolism by 50% to 60%.^{1,2} Although the risk of symptomatic venous thromboembolism, including fatal pulmonary

embolism, persists for 6 weeks or more after hospital discharge in high-risk medical patients, thromboprophylaxis extended after hospital discharge is not recommended by current practice guidelines.³ Recent clinical trials, when considered together, have unequivocally established the effectiveness of extended

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CLINICAL PERSPECTIVE

What Is New?

- Extended thromboprophylaxis in medically ill patients is not recommended by guidelines because of uncertainty about the benefit and concern about the risk of bleeding.
- Patients with acute medical illness are also at risk for myocardial infarction or ischemic stroke during the several weeks after hospital discharge; these outcomes have historically not been included in the benefit–risk assessment.
- Thromboprophylaxis extended after hospital discharge is effective for reducing the composite of major or fatal thromboembolic outcomes, which included both venous and arterial events; fatal or critical site bleeding events were infrequent and occurred in <0.1% of patients.

What Are the Clinical Implications?

- Implementation of extended thromboprophylaxis in appropriately selected patients could have a major population health impact in reducing the burden of venous and arterial thromboembolic disease.

Nonstandard Abbreviations and Acronyms

MAGELLAN Multicenter, randomized, parallel-group efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically ill patients comparing rivaroxaban with enoxaparin

MARINER Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolic Risk

thromboprophylaxis using a direct oral anticoagulant for preventing symptomatic venous thromboembolism when given for ≈25 to 45 days after hospital discharge.^{4–6} However, these trials did not demonstrate a reduction in fatal venous thromboembolism. Whether the benefits of extended thromboprophylaxis overall outweigh the risks remains controversial because of uncertainty about the benefit for preventing fatal thromboembolic events, and whether the risk of major bleeding offsets the benefit of reduced nonfatal symptomatic venous thromboembolism.

Patients hospitalized with acute medical illness are also at risk for fatal or irreversible atherothrombotic events such as myocardial infarction or ischemic stroke during the several weeks after hospital discharge.^{7–9}

These outcomes are also preventable by anticoagulant thromboprophylaxis,^{8,9} but historically, they have not been included in the benefit–risk calculations for extended thromboprophylaxis. Recent data suggest that extended thromboprophylaxis with prophylactic doses of the direct oral anticoagulant betrixaban may reduce this risk by ≈50%.^{7–9} Since the bleeding complications of anticoagulant thromboprophylaxis may be fatal or irreversible (eg, intracranial hemorrhage), it is clinically relevant to also consider all major or fatal thromboembolic outcomes, both venous and arterial, in assessing the overall benefit–risk balance with extended thromboprophylaxis.

The efficacy and safety of the 10-mg dose of rivaroxaban for thromboprophylaxis in patients hospitalized for acute medical illnesses and who were at risk for thromboembolic complications has been evaluated in 2 large randomized, double-blind clinical trials, MAGELLAN (Multicenter, randomized, parallel-group efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically ill patients comparing rivaroxaban with enoxaparin) and MARINER (Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolic Risk). We performed a pooled analysis of the data from these trials to (1) evaluate the benefit–risk profile of thromboprophylaxis compared with placebo in the postdischarge period for preventing all major or fatal thromboembolic outcomes, both venous and arterial; and (2) determine whether extended thromboprophylaxis provides a benefit in reducing all-cause mortality.

METHODS

Data Sharing Statement

At present, the sponsor's policy is to share data after regulatory approval in accordance with the policy of its co-development partner. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the criteria for listing studies and other relevant information is provided in the co-development partner's section of the portal.

Study Design

The primary results of the MAGELLAN and MARINER trials have been previously published.^{4,6} The institutional review board or ethics committee at each participating center approved the protocol and all the patients provided written informed consent. In brief, the MAGELLAN study (N=8101) evaluated prophylaxis with 10 mg of

rivaroxaban daily, begun in the hospital and continued for a total of 35 ± 4 days in acutely ill medical patients compared with enoxaparin (40 mg daily for 10 ± 4 days) followed by placebo. The primary end point was the composite of asymptomatic proximal deep vein thrombosis, symptomatic deep vein thrombosis, pulmonary embolism or venous thromboembolism (VTE)–related death. The MARINER study (N=12 019) evaluated prophylaxis with 10 mg of rivaroxaban daily (or 7.5 mg daily in patients with a baseline creatinine clearance [CrCl] 30 to <50 mL/min), begun at discharge from the hospital and continued for 45 days, compared with placebo, in acutely ill medical patients. All patients in the MARINER study had an acute medical condition that warranted thromboprophylaxis during the hospital stay and all received either low molecular weight heparin or unfractionated heparin before randomization. The primary end point was the composite of symptomatic VTE and VTE-related death through day 45. In both studies, if patients were re-admitted to the hospital during the outpatient phase of the trial, they were given prophylaxis against venous thromboembolism according to the judgment of the attending physician.

Both trials specified a priori that all suspected episodes of VTE, myocardial infarction, stroke, bleeding, and all deaths would be documented and adjudicated by the central independent clinical events committee, according to prespecified criteria.^{4,6} A key safety outcome in both trials was major bleeding, which included critical site (ie, intracranial, intraspinal,

intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal) or fatal bleeding.^{4,6}

Pooled Analysis

The analyses using the pooled data were defined post hoc. To test the hypothesis that thromboprophylaxis given after hospital discharge using 10 mg of rivaroxaban once daily can reduce fatal and major thromboembolic outcomes without substantially increasing critical site or fatal bleeding, we pooled patient-level data from the outpatient portion of the MAGELLAN trial (≈ 25 days of treatment) with the data from the MARINER trial (45 days of treatment). For the MAGELLAN trial, we included all patients who were alive and free from a thromboembolic or bleeding event up to the last dose of enoxaparin or matching placebo (ie, the in-hospital phase), and who continued in the outpatient, placebo-controlled phase of the trial. For the MARINER trial, we included all patients within the prerandomization stratum for a $\text{CrCl} \geq 50$ mL/min; these patients were randomized to receive 10 mg rivaroxaban once daily or placebo (Figure 1).⁶ We did not include patients within the stratum for a $\text{CrCl} < 50$ mL/min, who were randomized to receive either 7.5 mg of rivaroxaban or placebo, because the 7.5-mg dose was ineffective¹⁰ and is not licensed for clinical use for the primary prevention of venous thromboembolism. Efficacy outcomes for the pooled analyses included the composite of symptomatic deep-vein thrombosis,

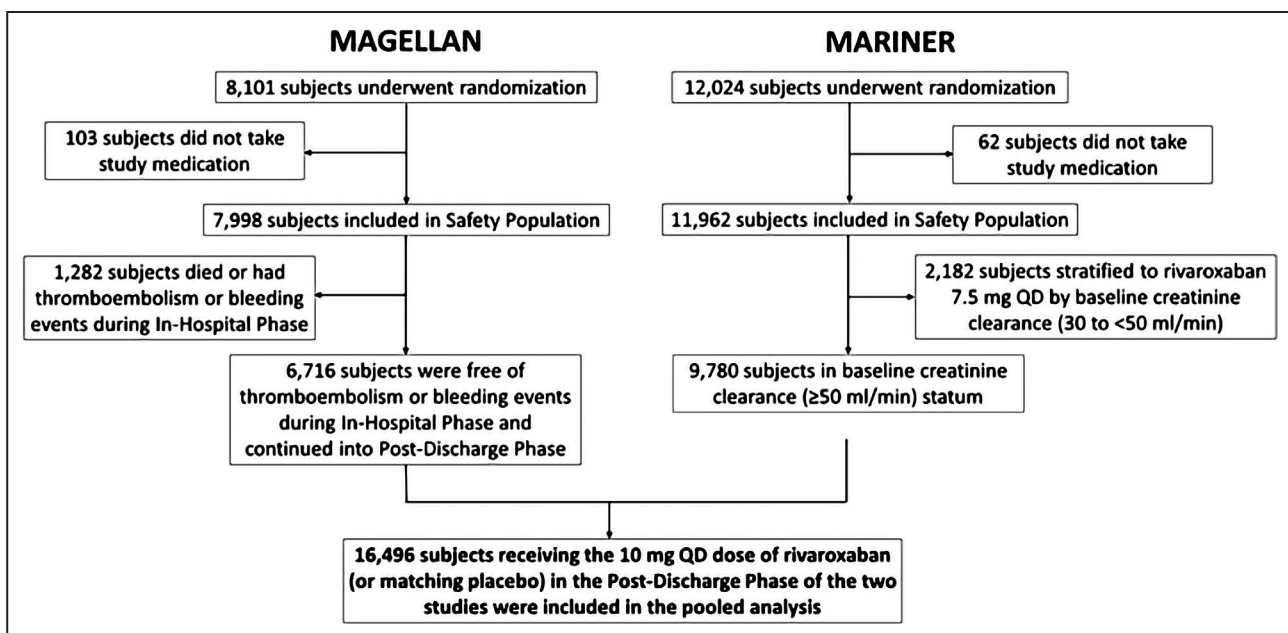


Figure 1. Pooled safety population of MAGELLAN and MARINER.

MAGELLAN indicates Multicenter, randomized, parallel-group efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically ill patients comparing rivaroxaban with enoxaparin; and MARINER, Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolic Risk.

nonfatal pulmonary embolism, myocardial infarction, nonhemorrhagic stroke, and all-cause mortality. All-cause mortality was also evaluated separately. Bleeding outcomes included fatal or critical site bleeding. There were no important adverse events other than bleeding.

The population for the pooled analysis was derived from the safety population for each study, which included all randomized patients who received at least 1 dose of study medication. For the efficacy analyses, the postdischarge period was defined as the period from 1 day after the last dose of enoxaparin (or matching placebo for subjects in rivaroxaban group) to Day 35 (+6) for patients in the MAGELLAN trial, and the period from randomization to Day 45 for patients in the MARINER trial.

For the safety analyses, the postdischarge period was defined as the period from 1 day after the last dose of enoxaparin (or matching placebo for subjects in rivaroxaban group) to 2 days after the last dose day of rivaroxaban/placebo (inclusive) for patients from the MAGELLAN study, and as the period from randomization to 2 days after the last dose of the study drug (inclusive) for patients from the MARINER study.

The statistical analysis was performed using the Cox proportional hazards model, stratified by study to allow the baseline hazard to vary across the 2 trials, with treatment as the only covariate and no other adjustment. The hazard ratio (HR) and its 95% CI, and the *P* value (2-sided) were determined for the composite outcome and its components. For benefit and risk, the 95% CI for the difference in event rates between the rivaroxaban and placebo groups was based on asymptotic methods. Our focus on excess number of events and number needed to treat (NNT)/ number needed to harm (NNH) for events that are fatal or cause irreversible harm is similar to that used for previous benefit–risk assessments.^{11–13} The NNT and NNH along with the 95% CI were calculated as the reciprocals of the absolute differences in risk of the efficacy and bleeding outcomes, respectively. Baseline demographic and clinical characteristics were analyzed by treatment group for each individual study and the pooled population.

RESULTS

Demographics and Clinical Characteristics

A total of 16 496 patients (8222 in rivaroxaban group, 8274 in placebo group) were included in the pooled analysis. The baseline demographics and clinical characteristics of the patients were similar in the 2 treatment groups (Table 1). The mean age was 68 years with the majority of the subjects having CrCl \geq 50 mL/min at baseline (91%). Heart failure was the most common reason for hospitalization, followed by acute infectious disease.

The plasma D-dimer value was greater than 2 times the upper limit of normal range in 58.5% of patients.

Efficacy Outcomes

The efficacy outcomes for the pooled analysis and for each study individually are shown in Table 2. For the composite of all symptomatic thromboembolic events (which included symptomatic deep vein thrombosis, nonfatal pulmonary embolism, myocardial infarction, and nonhemorrhagic stroke) and all-cause mortality, the incidence was 1.80% (148/8222 subjects) in the rivaroxaban group, compared with 2.31% (191/8274 subjects) in the placebo group. The HR for rivaroxaban versus placebo was 0.78 (95% CI, 0.63–0.97, *P*=0.024), representing a 22% relative risk reduction.

Death from any cause occurred in 105 (1.28%) of 8222 subjects in the rivaroxaban group and 118 (1.43%) of 8274 subjects in the placebo group (HR, 0.90 [95% CI, 0.69–1.17]; *P*=0.431). Death was adjudicated to be definitely because of pulmonary embolism in 2 (0.02%) patients in the rivaroxaban group, and in 2 patients (0.02%) in the placebo group; the cause of death was not definitively established and adjudicated as “venous thromboembolism cannot be excluded” in 35 patients in the rivaroxaban group (0.43%) and 42 patients (0.51%) in the placebo group.

Bleeding Outcomes

The bleeding outcomes for the pooled analysis and for each study individually are shown in Table 3. Fatal and critical site bleeding occurred in <0.1% of the subjects in both groups. The rate was numerically increased with rivaroxaban treatment (rivaroxaban 0.09% versus placebo 0.04%, HR, 2.36 [95% CI, 0.61–9.11], *P*=0.214). Of the total of 7 fatal or critical site bleeding events in the rivaroxaban group, 4 occurred within the first week of treatment, 0 occurred between 7 and 14 days, 1 between 14 and 21 days, and 2 after 21 days of treatment. The 3 fatal or critical site bleeding events in the placebo group occurred at 4, 7, and 8 days after randomization.

Benefit and Risk

For the composite outcome of all-cause mortality and major/irreversible thromboembolic outcomes, the NNT to prevent 1 event was 197 (95% CI, NNT 107–1323). The NNH to cause 1 additional fatal or critical site bleeding event was 2045 (95% CI, NNH 805 to ∞ to NNT 3798). In other words, for 10 000 patients treated with rivaroxaban versus placebo, on average there would be 51 fewer deaths or major/irreversible thromboembolic events and 5 more fatal or critical site bleeding events (a 10:1 benefit–risk ratio). These point estimates and 95% CI are shown in Figure 2.

Table 1. Baseline Demographics and Clinical Characteristics

	Pooled*		MAGELLAN†		MARINER‡	
	Rivaroxaban 10 mg QD n=8222 n	Placebo n=8274 n	Rivaroxaban 10 mg QD n=3332 n	Placebo n=3384 n	Rivaroxaban 10 mg QD n=4890 n	Placebo n=4890 n
Demographics						
Age, mean (y)	68.22	68.13	68.80	68.80	67.82	67.66
≥75 y	2542 (30.9%)	2563 (31.0%)	1213 (36.4%)	1262 (37.3%)	1329 (27.2%)	1301 (26.6%)
Sex, male	4557 (55.4%)	4507 (54.5%)	1853 (55.6%)	1781 (52.6%)	2704 (55.3%)	2726 (55.7%)
Race, White	7000 (85.1%)	7044 (85.1%)	2292 (68.8%)	2314 (68.4%)	4708 (96.3%)	4730 (96.7%)
Weight, mean (kg)	81.02	80.72	77.97	77.61	83.09	82.88
BMI, mean (kg)	29.06	28.91	28.37	28.35	29.53	29.29
Baseline clinical characteristics						
CrCl (mL/min)						
<30	45 (0.5%)	48 (0.6%)	45 (1.4%)	48 (1.4%)	0	0
30 to <50	623 (7.6%)	651 (7.9%)	621 (18.6%)	649 (19.2%)	2 (<0.1%)	2 (<0.1%)
≥50	7496 (91.2%)	7512 (90.8%)	2608 (78.3%)	2624 (77.5%)	4888 (>99.9%)	4888 (>99.9%)
Missing	58 (0.7%)	63 (0.8%)	58 (1.7%)	63 (1.9%)	0	0
Heart failure	2951 (35.9%)	2945 (35.6%)	1117 (33.5%)	1134 (33.5%)	1834 (37.5%)	1811 (37.0%)
Acute ischemic stroke	1342 (16.3%)	1359 (16.4%)	583 (17.5%)	590 (17.4%)	759 (15.5%)	769 (15.7%)
Acute infectious disease	2366 (28.8%)	2340 (28.3%)	1491 (44.7%)	1483 (43.8%)	875 (17.9%)	857 (17.5%)
Inflammatory disease	191 (2.3%)	203 (2.5%)	117 (3.5%)	121 (3.6%)	74 (1.5%)	82 (1.7%)
Acute respiratory insufficiency	2225 (27.1%)	2327 (28.1%)	879 (26.4%)	956 (28.3%)	1346 (27.5%)	1371 (28.0%)
History of VTE	817 (9.9%)	792 (9.6%)	152 (4.6%)	135 (4.0%)	665 (13.6%)	657 (13.4%)
History of cancer	939 (11.4%)	968 (11.7%)	552 (16.6%)	540 (16.0%)	387 (7.9%)	428 (8.8%)
ICU or CCU stay	2941 (35.8%)	2934 (35.5%)	252 (7.6%)	269 (7.9%)	2689 (55.0%)	2665 (54.5%)
Current lower-limb paralysis or paresis	1522 (18.5%)	1540 (18.6%)	553 (16.6%)	566 (16.7%)	969 (19.8%)	974 (19.9%)
D-dimer>2X ULN	4799 (58.4%)	4846 (58.6%)	1435 (43.1%)	1482 (43.8%)	3364 (68.8%)	3364 (68.8%)

CCU indicates critical care unit; CrCl, creatinine clearance; ICU, Intensive Care Unit; ULN, upper limit of normal; and VTE, venous thromboembolism.

*Pooled analysis set as defined in Methods section.

†Safety analysis set of MAGELLAN including only subjects who were free of thrombotic or bleeding events up to the last dose of enoxaparin or matching placebo and continued in the outpatient phase.

‡Safety analysis set of the MARINER 10-mg dose stratum.

DISCUSSION

The results of our pooled analysis suggest 3 key inferences. First, thromboprophylaxis extended for ≈25 to 45 days after hospital discharge is effective for reducing the composite of major or fatal thromboembolic outcomes, which included both venous and arterial events, among patients hospitalized for acute medical illness and who were assessed to be at increased risk of venous thromboembolism. Second, although a statistically significant reduction in all-cause mortality was not detected, a clinically important potential benefit for this outcome cannot be excluded. Third, the absolute risk of fatal or critical site bleeding was low (9 per 10 000 patients), indicating that with appropriate patient selection, extended thromboprophylaxis can be administered with acceptable safety, overcoming a key concern that has limited adoption of extended thromboprophylaxis in the past. The clinical and population

health implications of each of these inferences are discussed in turn below.

The regimen of rivaroxaban of 10 mg once daily was associated with a 22% relative risk reduction in the composite outcome of symptomatic deep-vein thrombosis or nonfatal pulmonary embolism, myocardial infarction, nonhemorrhagic stroke, and death from all causes. The absolute risk difference in this outcome of major or fatal thromboembolic events was 0.51%, corresponding to a NNT to prevent 1 event of 197. The risk difference of 0.51% is clinically important, given the severity of these major or fatal events. The NNT of 197 (95% CI, NNT: 107–1323) indicates an important population health impact of thromboprophylaxis for reducing the serious disease burden and health care resource utilization caused by these thromboembolic events. This NNT compares favorably with other clinical preventive measures commonly used in current practice; for example, the NNT to prevent 1 stroke with

Table 2. Efficacy Outcomes

Outcome	Rivaroxaban 10 mg QD	Placebo	Rivaroxaban vs Placebo	
	n (%)	n (%)	Hazard ratio (95% CI)	Nominal P value [§]
Pooled analyses*	n=8222	n=8274		
Composite of ACM, symptomatic DVT, nonfatal PE, MI, nonhemorrhagic stroke	148 (1.80)	191 (2.31)	0.78 (0.63, 0.97)	0.024
ACM	105 (1.28)	118 (1.43)	0.90 (0.69, 1.17)	0.431
Composite of symptomatic DVT, nonfatal PE, MI, nonhemorrhagic stroke	52 (0.63)	83 (1.00)	0.63 (0.45, 0.89)	0.009
Symptomatic DVT	7 (0.09)	19 (0.23)	0.37 (0.16, 0.88)	0.025
Nonfatal PE	4 (0.05)	19 (0.23)	0.21 (0.07, 0.62)	0.005
MI	23 (0.28)	13 (0.16)	1.78 (0.90, 3.52)	0.096
Nonhemorrhagic stroke	20 (0.24)	36 (0.44)	0.56 (0.32, 0.96)	0.037
MAGELLAN [†]	n=3332	n=3384		
Composite of ACM, symptomatic DVT, nonfatal PE, MI, nonhemorrhagic stroke	79 (2.37)	87 (2.57)	0.93 (0.68, 1.26)	0.622
ACM	60 (1.80)	58 (1.71)	1.06 (0.74, 1.52)	0.765
Composite of symptomatic DVT, nonfatal PE, MI, nonhemorrhagic stroke	21 (0.63)	32 (0.95)	0.67 (0.39, 1.16)	0.152
Symptomatic DVT	5 (0.15)	8 (0.24)	0.64 (0.21, 1.95)	0.430
Nonfatal PE	0 (0.00)	8 (0.24)	NA	NA
MI	10 (0.30)	5 (0.15)	2.04 (0.70, 5.97)	0.193
Nonhemorrhagic stroke	7 (0.21)	12 (0.35)	0.60 (0.23, 1.51)	0.276
MARINER [‡]	n=4890	n=4890		
Composite of ACM, symptomatic DVT, nonfatal PE, MI, nonhemorrhagic stroke	69 (1.41)	104 (2.13)	0.66 (0.49, 0.90)	0.008
ACM	45 (0.92)	60 (1.23)	0.75 (0.51, 1.10)	0.144
Composite of symptomatic DVT, nonfatal PE, MI, nonhemorrhagic stroke	31 (0.63)	51 (1.04)	0.61 (0.39, 0.95)	0.028
Symptomatic DVT	2 (0.04)	11 (0.22)	0.18 (0.04, 0.82)	0.026
Nonfatal PE	4 (0.08)	11 (0.22)	0.36 (0.12, 1.14)	0.083
MI	13 (0.27)	8 (0.16)	1.62 (0.67, 3.92)	0.281
Nonhemorrhagic stroke	13 (0.27)	24 (0.49)	0.54 (0.28, 1.06)	0.074

ACM indicates all-cause mortality; DVT, deep vein thrombosis; MI, myocardial infarction; NA, not applicable; MAGELLAN, Multicenter, randomized, parallel-group efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically ill patients comparing rivaroxaban with enoxaparin; MARINER, Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolic Risk; and PE, pulmonary embolism.

*Pooled analysis set as defined in Methods section.

[†]Safety analysis set of MAGELLAN including only subjects who were free of thrombotic or bleeding events up to the last dose of enoxaparin or matching placebo and continued in the outpatient phase.

[‡]Safety analysis set of the MARINER 10-mg dose stratum.

[§]P value (2-sided) for superiority of rivaroxaban versus placebo from the Cox proportional hazards model.

the use of the direct oral anticoagulant apixaban instead of warfarin is ≈ 330 .¹⁴

The composite outcome of fatal bleeding or bleeding into a critical site occurred in 7 of 8222 patients (0.09%) who received rivaroxaban, compared with 3 of 8247 patients (0.04%) given placebo (risk difference, 0.05%). This difference in risk is 10-fold less than the risk difference for thromboembolic events and corresponds to an NNH of 2045 (95% CI, NNH 805 to ∞ to NNT 3798). The ratio of the NNT to prevent 1 thromboembolic event (NNT 197) to the NNH

for 1 bleeding event (2045) indicates that the implementation of extended thromboprophylaxis with rivaroxaban in appropriately selected patients is expected to prevent 10 major or fatal thromboembolic events for each similarly severe bleeding event that is caused. This benefit–risk relationship favors the use of thromboprophylaxis, especially given the irreversible or fatal nature of the thromboembolic events that are prevented. The analysis is consistent with 2 recent reports that reveal a reduction of major and fatal or irreversible cardiovascular events using extended

Table 3. Bleeding Outcomes

Outcome	Rivaroxaban 10 mg QD	Placebo	Rivaroxaban vs Placebo	
	n (%)	n (%)	Hazard ratio (95% CI)	Nominal <i>P</i> value [§]
Pooled analyses*	n=8222	n=8274		
Fatal or critical site bleeding	7 (0.09)	3 (0.04)	2.36 (0.61, 9.11)	0.214
Fatal bleeding	4 (0.05)	0	NA	NA
Critical site bleeding	6 (0.07)	3 (0.04)	2.02 (0.51, 8.08)	0.320
MAGELLAN†	n=3332	n=3384		
Fatal or critical site bleeding	4 (0.12)	1 (0.03)	4.08 (0.46, 36.49)	0.209
Fatal bleeding	2 (0.06)	0	NA	NA
Critical site bleeding	4 (0.12)	1 (0.03)	4.08 (0.46, 36.49)	0.209
MARINER‡	n=4890	n=4890		
Fatal or critical site bleeding	3 (0.06)	2 (0.04)	1.50 (0.25, 8.98)	0.657
Fatal bleeding	2 (0.04)	0	NA	NA
Critical site bleeding	2 (0.04)	2 (0.04)	1.00 (0.14, 7.10)	1.000

MAGELLAN indicates Multicenter, randomized, parallel-group efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically ill patients comparing rivaroxaban with enoxaparin; MARINER, Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolic Risk; and NA, not applicable.

*Pooled analysis set as defined in Methods section.

†Safety analysis set of MAGELLAN including only subjects who were free of thrombotic or bleeding events up to the last dose of enoxaparin or matching placebo and continued in the outpatient phase.

‡Safety analysis set of the MARINER 10-mg dose stratum.

§*P* value (2-sided) for superiority of rivaroxaban versus placebo from the Cox proportional hazards model.

thromboprophylaxis with betrixaban and rivaroxaban in medically ill patients.^{9,15}

Historically, the primary reason for using thromboprophylaxis in acutely ill medical patients has been to prevent death from pulmonary embolism. More recently, studies have found that patients hospitalized for acute medical illness are also at risk of developing major or fatal arterial thromboembolic events such as ischemic stroke or myocardial infarction during the 4 to 6 weeks after discharge.^{7–9} From the patient's perspective, these arterial thromboembolic events are also important in terms of survival and quality of life. The approach of considering both major venous and arterial thromboembolic events and major bleeding complications of similar clinical severity and that are strongly associated with all-cause mortality provides a more balanced and patient-centered perspective for evaluating the benefit–risk of extended thromboprophylaxis. The outcomes of symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, and nonhemorrhagic stroke were all statistically significantly lower in the rivaroxaban group, with relative risk reductions of 63%, 79%, and 44%, respectively (Table 2). The outcome of myocardial infarction was observed more frequently in the rivaroxaban group but this difference was not statistically significant (Table 2), and the 95% CI for the HR includes a possible 10% relative risk reduction in favor of rivaroxaban. Whether this represents a truly different effect of rivaroxaban on the arterial thromboembolism outcomes of stroke and myocardial infarction, or only chance variation is unknown.

The current COVID-19 pandemic has resulted in a surge of hospitalizations of medically ill patients worldwide. The disease appears to be associated with a coagulopathy that increases the likelihood of both arterial and venous thrombotic events.¹⁶ A significant portion of hospitalized patients with COVID-19 with viral pneumonia have elevated D-dimer at baseline, which has been associated with more severe disease and poor outcomes including mortality.^{17,18} Extended thromboprophylaxis with rivaroxaban has been shown to be superior to standard dose in-hospital enoxaparin in the subgroup of patients with infectious disease as the cause for hospitalization with the most common infection being pneumonia,¹⁹ and with those with elevated D-dimer.²⁰ Taken together with the results of this pooled analysis, these data would suggest that extended thromboprophylaxis with a direct oral Factor Xa inhibitor postdischarge might be of particular use in limiting thrombotic complications associated with COVID-19. Although the anticoagulation coronavirus (ACTION) trial²¹ in a hospitalized COVID-19 population using elevated D-dimer criteria did not detect a clinical benefit of in-hospital plus extended treatment dose thromboprophylaxis with rivaroxaban given for 30 days (20 mg daily) compared with standard of care in-hospital thromboprophylaxis, the Medically Ill Hospitalized Patients for COVID-19 Thrombosis Extended Prophylaxis with Rivaroxaban Therapy (MICHELLE) trial²² (ClinicalTrials.gov NCT04662684), using the same postdischarge randomization design

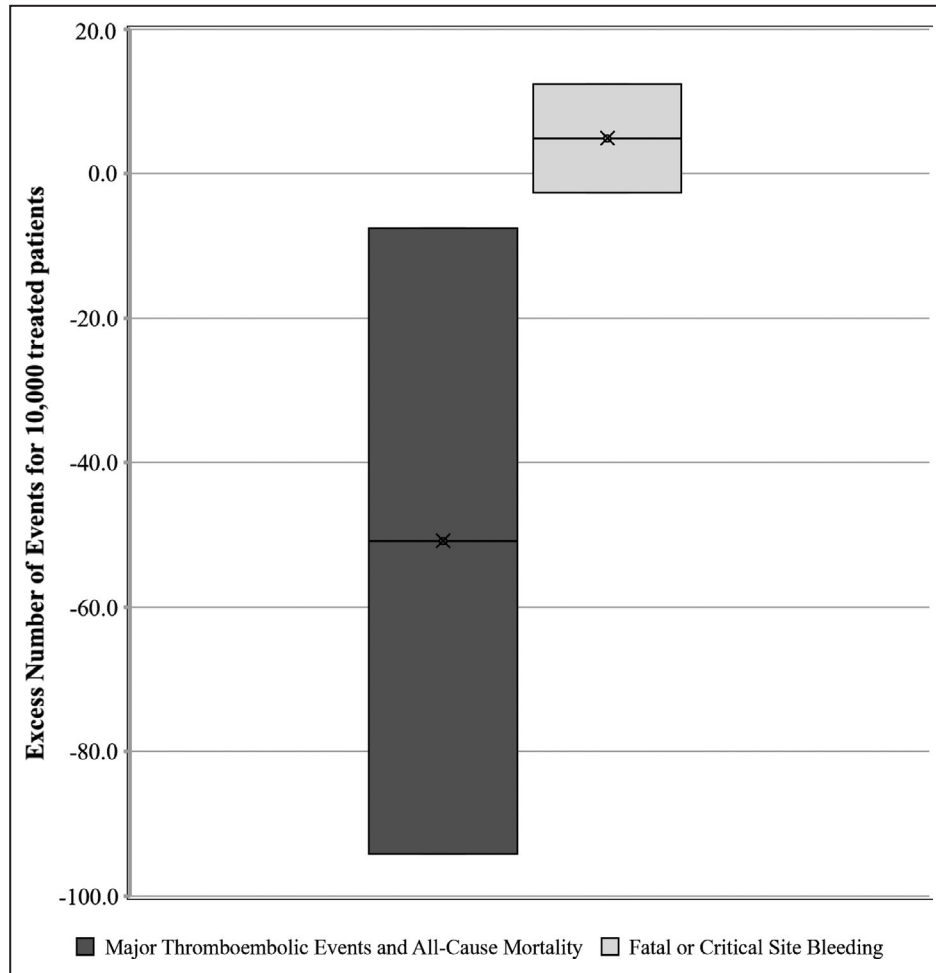


Figure 2. Major thromboembolic events and deaths prevented and critical site or fatal bleeding events caused (X) and 95% CI (bars) for rivaroxaban compared with placebo for a population of 10 000 treated patients.

and enrichment criteria as the MARINER trial, did reveal a significant 67% relative risk reduction (9.43%–3.14%, relative risk, 0.33 [95% CI 0.12–0.90], $P=0.029$) of major and fatal venous and arterial thromboembolic events favoring rivaroxaban 10 mg daily over no anticoagulation at Day 35 post-hospital discharge.²³ The COVID-19 Post-hospital Thrombosis Prevention Trial: An Adaptive, Multicenter, Prospective, Randomized Platform Trial Evaluating the Efficacy and Safety of Antithrombotic Strategies in Patients With COVID-19 Following Hospital Discharge (ACTIV-4C) trial is evaluating the benefit–risk of thromboprophylaxis using apixaban 2.5 mg given for 30 days after hospital discharge in 5320 patients with COVID-19 (ClinicalTrials.gov NCT04650087).

Our analysis has some limitations. The analysis was post hoc, and the selection of patients for inclusion from the MAGELLAN study was done after randomization. However, the treatment groups from the individual studies, as well as the pooled population,

were comparable for demographic and baseline clinical characteristics (Table 1). Despite a sample size of >16 000 patients, the analysis could neither confirm nor exclude a clinically important effect for reducing death from all causes. The observed relative risk reduction for all-cause mortality was 10%. This result is similar to the relative risk reduction in all-cause mortality observed in patients with atrial fibrillation who are given direct oral anticoagulants for preventing stroke and systemic embolism.²⁴ Our results are not generalizable to patients with moderate to severe renal insufficiency (CrCl <50 mL/min), which represents ~35% of hospitalized medical patients.²⁵ Further research is needed to improve the benefit–risk of thromboprophylaxis in this subgroup of patients. A recent analysis of the MAGELLAN study suggests that a positive benefit–risk profile can be achieved in a subset of these patients with appropriate patient selection.¹⁰ An additional limitation to generalizability is that patient selection in the MARINER trial included

an assessment of plasma D-dimer, which may not be routine practice in all hospitals, although it has been validated as an important biomarker in hospitalized patients with COVID-19.^{26,27} Furthermore, our analysis assumes that major or fatal thromboembolic outcomes and critical-site or fatal bleeding outcomes are weighted equally, and different patients may have different values and preferences for these outcomes, which may influence the decision to give extended thromboprophylaxis. The NNH values used in our benefit–risk assessment are based on observed differences in bleeding (Table 3), which were not statistically significant, and it is possible that these differences reflect chance variation and not a true increased risk with rivaroxaban. Finally, our analysis did not include nonfatal or noncritical site major bleeding or nonmajor bleeding in the benefit–risk assessment, and these outcomes may also be relevant for some patients or clinicians in assessing benefit–risk.

CONCLUSIONS

In conclusion, for patients admitted to the hospital with acute medical illness, rivaroxaban 10 mg once daily given for ≈25 to 45 days after hospital discharge is effective for preventing major or fatal thromboembolic events, with a low risk of fatal or critical site bleeding. Given that there are at least 7.2 million patients with medical illness who are hospitalized each year in the United States at risk for VTE,²⁸ widespread implementation of extended thromboprophylaxis in appropriately selected patients could have a major population health impact in reducing the burden of venous and arterial thromboembolic disease.

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REFERENCES

1. Spyropoulos AC, Raskob GE. New paradigms in venous thromboprophylaxis of medically ill patients. *Thromb Haemost*. 2017;117:1662–1670. doi: 10.1160/TH17-03-0168
2. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis. 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e419S–e496S. doi: 10.1378/chest.11-2301
3. Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, Rezende SM, Zakai NA, Bauer KA, Dentali F, 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. doi: 10.1182/bloodadvances.2018022954
4. Cohen AT, Spiro TE, Büller HR, Haskell L, Hu D, Hull R, Mebazaa A, Merli G, Schellong S, Spyropoulos AC, et al.; MAGELLAN Investigators. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368:513–523. doi: 10.1056/NEJMoa1111096
5. Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, Gold A, Hernandez AF, Gibson CM, Investigators APEX. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med*. 2016;375:534–544. doi: 10.1056/NEJMoa1601747
6. Spyropoulos AC, Ageno W, Albers GW, Elliott CG, Halperin JL, Hiatt WR, Maynard GA, Steg PG, Weitz JI, Suh E, et al. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. *N Engl J Med*. 2018;379:1118–1127. doi: 10.1056/NEJMoa1805090
7. Nafee T, Gibson CM, Yee MK, Kerneis M, Daaboul Y, Korjian S, Chi G, Kalayci A, Afzal MK, Kazmi H, et al. Reduction of cardiovascular mortality and ischemic events in acute medically ill patients. *Circulation*. 2019;139:1234–1236. doi: 10.1161/CIRCULATIONAHA.118.038654
8. Gibson CM, Chi G, Halaby R, Korjian S, Daaboul Y, Jain P, Arbetter D, Goldhaber SZ, Hull R, Hernandez AF, 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;135:648–655. doi: 10.1161/CIRCULATIONAHA.116.025427
9. Gibson CM, Korjian S, Chi G, Daaboul Y, Jain P, Arbetter D, Goldhaber SZ, Hull R, Hernandez AF, Lopes RD, 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:e006015. doi: 10.1161/JAHA.117.006015
10. Weitz JI, Raskob GE, Spyropoulos AC, Spiro TE, De Sanctis Y, Xu J, Lu W, Suh E, Argenti D, Yang H, et al. Thromboprophylaxis with rivaroxaban in acutely ill medical patients with renal impairment: insights from the MAGELLAN and MARINER trials. *Thromb Haemost*. 2020;120:515–524. doi: 10.1055/s-0039-1701009
11. Unger EF. Weighing benefits and risks – the FDA’s review of Prasugrel. *N Engl J Med*. 2009;361:942–945. doi: 10.1056/NEJMp0907122
12. Beasley BN, Unger EF, Temple R. Anticoagulant options – why the FDA approved a higher but not a lower dose of dabigatran. *N Engl J Med*. 2011;364:1788–1790. doi: 10.1056/NEJMp1103050

13. Gibson CM, Levitan B, Gibson WJ, Yee MK, Murphy SA, Yuan Z, Chakrabarti AK, Lee M, Braunwald E. Fatal or irreversible bleeding and ischemic events with rivaroxaban in acute coronary syndrome. *J Am Coll Cardiol*. 2018;72:129–136. doi: 10.1016/j.jacc.2018.04.055
14. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al.; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992. doi: 10.1056/NEJMoa1107039
15. Spyropoulos AC, Ageno W, Albers GW, Elliott CG, Halperin JL, Hiatt WR, Maynard GA, Steg PG, Weitz JI, Lu W, 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. doi: 10.1016/j.jacc.2020.04.071
16. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian CD, Ageno W, Madjid M, Guo Y, et al. Global COVID-19 thrombosis collaborative group, endorsed by the ISTH, NATF, ESVM, and the IUA, supported by the ESC working group on pulmonary circulation and right ventricular function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. 2020;75:2950–2973. doi: 10.1016/j.jacc.2020.04.031
17. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062. doi: 10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11. Erratum in: *Lancet*. 2020;395(10229):1038
18. Cohen SL, Gianos E, Barish MA, Chatterjee S, Kohn N, Lesser M, Giannis D, Coppa K, Hirsch JS, McGinn TG, et al.; Northwell Health COVID-19 Research Consortium. Prevalence and predictors of venous thromboembolism or mortality in hospitalized COVID-19 patients. *Thromb Haemost*. 2021;121:1043–1053. doi: 10.1055/a-1366-9656
19. Cohoon KP, De Sanctis Y, Haskell L, McBane RD, Spiro TE. Rivaroxaban for thromboprophylaxis among patients recently hospitalized for acute infectious diseases: a subgroup analysis of the MAGELLAN study. *J Thromb Haemost*. 2018;16:1278–1287. doi: 10.1111/jth.14146
20. Spyropoulos AC, Lipardi C, Xu J, Peluso C, Spiro TE, De Sanctis Y, Barnathan ES, Raskob GE. Modified IMPROVE VTE risk score and elevated d-dimer identify a high venous thromboembolism risk in acutely ill medical population for extended thromboprophylaxis. *Thrombosis Haemostasis Open*. 2020;4:e59–e65. doi: 10.1055/s-0040-1705137
21. Lopes R, de Barros e Silva PGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, Barbosa LM, de Aveiro Morata J, Ramacciotti E, de Aquino Martins P, et al.; ACTION Coalition COVID-19 Brazil IV Investigators. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicenter, randomized, controlled trial. *Lancet*. 2021;397:2253–2263. doi: 10.1016/S0140-6736(21)01203-4
22. Ramacciotti E, Agati LB, Calderaro D, Volpiani GG, de Oliveira CCC, Aguiar VCR, Rodrigues E, Sobreira ML, Joviliano EE, Dusilek C, et al. Medically ill hospitalized patients for COVID-19 THrombosis Extended Prophylaxis with rivaroxaban ThErapy: rationale and design of the MICHELLE trial. *Am Heart J*. 2021;242:115–122. doi: 10.1016/j.ahj.2021.08.016
23. Ramacciotti E, Agati LB, Calderaro D, Aguiar VCR, Spyropoulos AC, Volpiani GG, de Oliveira CCC, Aguiar VCR, Rodrigues E, Sobreira ML & Joviliano EE et al. Medically ill hospitalized patients for COVID-19 thrombosis extended prophylaxis with rivaroxaban therapy: The MICHELLE Trial. Presented at European Society of Cardiology 2021 meeting. Available at: <https://pubmed.ncbi.nlm.nih.gov/34480880/>
24. Mant J, Hobbs FD, Fletcher K, Decousus H, Pini M, Chong BH, Zotz RB, Bergmann JF, Tapson V, Froehlich JB, et al.; IMPROVE Investigators. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007;370:493–503. doi: 10.1016/S0140-6736(07)61233-1
25. Spyropoulos AC, Anderson FA, FitzGerald G, Decousus H, Pini M, Chong BH, Zotz RB, Bergmann J-F, Tapson V, Froehlich JB, et al.; IMPROVE Investigators. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest*. 2011;140:706–714. doi: 10.1378/chest.10-1944
26. Spyropoulos AC, Giannis D, Goldin M. Vascular thromboembolic events following COVID-19 hospital discharge: incidence and risk factors. *Res Pract Thromb Haemost*. 2021;5:e12547. doi: 10.1002/rth2.12547
27. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, Mignatti A, Gianos E, Cohen M, Sharifova G, et al. HEP-COVID investigators. Efficacy and safety of therapeutic-dose Heparin vs standard prophylactic or intermediate-dose Heparins for Thromboprophylaxis in high-risk hospitalized patients With COVID-19: The HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021. doi: 10.1001/jamainternmed.2021.6203. Epub ahead of print.
28. Anderson FA Jr, Zayaruzny M, Heit JA, Fidan D, Cohen AT. Estimated annual numbers of US acute-care hospital patients at risk for venous thromboembolism. *Am J Hematol*. 2007;82:777–782. doi: 10.1002/ajh.20983