Thromboprophylaxis with Rivaroxaban in Acutely Ill Medical Patients with Renal Impairment: Insights from the MAGELLAN and MARINER Trials

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Abstract

Patients with renal impairment are at higher risk of thrombosis and bleeding than those with normal renal function. The optimal rivaroxaban dose for thromboprophylaxis in acutely ill medical patients with renal impairment is unknown. MARINER and MAGELLAN were multicenter, randomized clinical trials of rivaroxaban in acutely ill medical patients. Efficacy and safety outcomes in patients with renal impairment in MARINER (7.5 mg once daily) were compared with those in patients with normal renal function in MARINER (10 mg once daily) and in a subpopulation of MAGELLAN that excluded patients at high risk for bleeding at baseline (10 mg once daily). Compared with enoxaparin/placebo in the MAGELLAN subpopulation, the relative risk (RR) of symptomatic venous thromboembolism (VTE) and VTE-related death with rivaroxaban 10 mg in patients with renal impairment (RR = 0.62; 95% confidence interval [CI] 0.27–1.44) was similar to that in those with normal renal function (RR = 0.78; 95% CI 0.44–1.40), while in MARINER, the 7.5 mg dose did not reduce the risk in patients with renal impairment (hazard ratio = 1.00; 95% CI 0.52–1.92). Major bleeding with rivaroxaban 10 mg once daily was higher in patients with renal impairment than in those with normal renal function in MAGELLAN (1.54% vs. 0.98%) and in the MAGELLAN subpopulation (0.94% vs. 0.61%). At a dose of 10 mg once daily,

Keywords
► anticoagulants
► medically ill
► renal impairment
► venous thromboembolism
► rivaroxaban

rivaroxaban is effective for thromboprophylaxis in acutely ill medical patients with impaired or normal renal function. The safety of this regimen is enhanced without loss of efficacy by excluding patients at high risk for bleeding, but not by using a reduced-dose strategy.

Trial Registration   ClinicalTrials.gov identifiers: NCT00571649 for the MAGELLAN trial, NCT02111564 for the MARINER trial.

Introduction

Acutely ill medical patients are at risk of venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). At least 65% of fatal PE occur in medical patients,[1] who remain at risk for VTE for at least 3 months after discharge from hospital.[2,3] Guidelines recommend in-hospital thromboprophylaxis for medical patients with heart failure or severe respiratory disease, or for those confined to bed with additional risk factors such as infection, inflammatory disease, stroke, or prior VTE.[4,5] Balancing the benefits and risks of anticoagulant thromboprophylaxis is difficult in patients with renal impairment because they have hemostatic abnormalities that increase their risk of thrombosis and bleeding.[6] Furthermore, anticoagulants such as enoxaparin and rivaroxaban are cleared via the kidneys, which may lead to drug accumulation and bleeding in patients with impaired renal function.[7] Therefore, there remains a need for strategies that render anticoagulant thromboprophylaxis in acutely ill medical patients as effective and safe in patients with renal impairment as it is in those with normal renal function.

To identify the optimal dose of rivaroxaban for thromboprophylaxis in acutely ill medical patients with impaired renal function, we used data from the MAGELLAN and MARINER trials.[8,9] MAGELLAN compared rivaroxaban with enoxaparin during the in-hospital phase and with placebo for extended thromboprophylaxis, whereas MARINER compared rivaroxaban with placebo only in the outpatient phase. Rivaroxaban was administered at a dose of 10 mg once daily in both studies, but in the MARINER trial, the dose was reduced to 7.5 mg once daily in patients with renal impairment (creatinine clearance 30–49 mL/min). Incidences of VTE and bleeding in patients with renal impairment were compared with those in patients with normal renal function in all patients and in a subpopulation of those in the MAGELLAN trial, which excluded patients with risk factors for major bleeding using the exclusion criteria employed in the MARINER trial.

Methods

Study Population

We included patients enrolled in the previously reported MAGELLAN and MARINER trials.[8–11] Patients had to have a creatinine clearance of 30 mL/min or higher to be enrolled. The MAGELLAN trial (NCT00571649) was a multicenter, randomized, double-blind, parallel-group efficacy and safety study comparing oral rivaroxaban (10 mg once daily) administered for 35 ± 4 days with subcutaneous enoxaparin (40 mg once daily) administered for 10 ± 4 days followed by placebo for thromboprophylaxis in hospitalized acutely ill medical patients. Eligible patients included those at least 40 years of age who were hospitalized for an acute medical illness (i.e., heart failure, active cancer, acute ischemic stroke, acute infectious and inflammatory disease, and acute respiratory insufficiency) and were at risk for VTE because of immobility, or had additional risk factors such as age ≥ 75 years, history of cancer, history of VTE, history of heart failure, thrombophilia, acute infectious disease contributing to the hospitalization, and body mass index ≥ 35 kg/m². The MARINER trial (NCT02111564) was a multicenter, randomized, double-blind, parallel-group efficacy and safety study that compared rivaroxaban with placebo for out-of-hospital thromboprophylaxis in acutely ill medical patients discharged from hospital. Patients were stratified at baseline by renal function; subjects with normal renal function (i.e., creatinine clearance ≥ 50 mL/min) received rivaroxaban 10 mg once daily (or placebo), while those with renal impairment (i.e., creatinine clearance 30–49 mL/min) received rivaroxaban 7.5 mg once daily (or placebo). Treatments were given for 45 days. In all patients, creatinine clearance was measured before randomization using the Cockcroft–Gault formula.[12] Eligible patients were those at least 40 years of age, hospitalized for an acute medical illness (i.e., heart failure, acute ischemic stroke, acute infectious and inflammatory disease, and acute respiratory insufficiency), and at high risk of VTE based on a modified International Medical Prevention Registry on VTE (IMPROVE) risk assessment model score of 4 or more (or a score of 2 or 3 with a D-dimer level > 2 times the upper limit of normal). The MARINER trial excluded patients with risk factors for major bleeding including five key exclusionary criteria: active cancer at randomization, medical history of bronchiectasis or pulmonary cavitation, use of dual antiplatelet therapy at baseline, active gastroduodenal ulcer, or any bleeding in the 3 months prior to randomization. The previously described subpopulation of MAGELLAN excluded approximately 20% of patients with the risk factors for major bleeding used to exclude patients in MARINER.[13] Demographic data and clinical characteristics across the three populations were reported by baseline creatinine clearance.

Efficacy and Safety Outcomes

The incidences of VTE and bleeding in patients with and without renal impairment were compared in MAGELLAN, in the MAGELLAN subpopulation, and in MARINER. The primary efficacy outcome in the MAGELLAN trial was the composite of asymptomatic proximal DVT detected by mandatory bilateral

lower extremity venous ultrasonography, symptomatic VTE, and VTE-related death. All suspected events were adjudicated by committees blinded to treatment assignment. In the MARINER trial, the primary efficacy outcome was the composite of symptomatic VTE and VTE-related death as adjudicated by a committee blinded to treatment assignment. The incidence of asymptomatic proximal DVT was not assessed in MARINER. The primary safety outcome of MAGELLAN was treatment-emergent clinically relevant bleeding defined as the composite of major and clinically relevant nonmajor bleeding, while the primary safety outcome of MARINER was major bleeding. All suspected bleeding events were adjudicated and classified using the International Society on Thrombosis and Haemostasis criteria.[14]

Pharmacokinetics

In the MARINER study, two samples for pharmacokinetic (PK) analysis were obtained on day 7 (predose and 1–4 hours postdose). Another two samples were obtained on day 21 (3–7 and 7–12 hours postdose). In the MAGELLAN study, blood samples for PK and coagulation evaluation were obtained on day 1 (predose and 1, 2, 3, 4, 6, 9, and 12 hours postdose) and on day 10 ± 4 days (predose and 1, 2, 3, 4, 6, 9, and 12 hours postdose). The plasma rivaroxaban concentrations were determined using a validated liquid chromatography-tandem mass spectrometry method. Only concentrations above the lower limit of quantification (0.5 ng/mL) were included in the subsequent population PK analysis. The population PK model for rivaroxaban used in this analysis was developed previously[15] in patients with acute symptomatic DVT from the phase IIb clinical studies and a study in total hip replacement.[16,17] The new PK parameter estimates, such as steady-state area under the concentration curve (AUCss) and steady-state maximal concentration, for the current MARINER and MAGELLAN population were used to generate the empirical Bayesian (individual) predictions for all observations. Based upon individual plasma rivaroxaban concentration versus time data in patients taking the 7.5 or 10 mg dose of rivaroxaban, the PKs and rivaroxaban exposure were derived using population PK modeling and were reported based on the baseline creatinine clearance.

Statistical Analysis

Demographic and clinical characteristics were reported according to treatment group and baseline creatinine clearance for the safety population, which included all randomized patients who received at least one dose of study medication. In the MAGELLAN trial, the efficacy analysis for total (asymptomatic and symptomatic) VTE and VTE-related death focused on the modified intent-to-treat population, which included all randomized patients who received at least one dose of study medication and had adequate ultrasonographic assessment of the proximal deep veins of the legs or symptomatic nonfatal or fatal VTE. Efficacy analyses for symptomatic VTE and VTE-related death were conducted in the safety population. In the MARINER trial, efficacy analysis for symptomatic VTE and VTE-related death focused on the intention-to-treat population, which included all randomized patients who provided valid informed consent.

Efficacy and safety analyses were performed using the study definitions, data rules, and derivations outlined in the MAGELLAN and MARINER Statistical Analysis Plans. Briefly, the relative risks (RRs) and their corresponding 95% confidence interval (CI) were calculated using the Mantel–Haenszel method[18] for MAGELLAN and the hazard ratios and their corresponding 95% CIs were calculated using the Cox proportional hazards model[19] for MARINER.

Results

Demographics and Clinical Characteristics

MAGELLAN randomized 8,101 patients from 562 sites in 52 countries.[8] The MAGELLAN safety population included 7,998 patients. With the retrospective use of five key bleeding risk factors, 1,551 patients were excluded from MAGELLAN and the remaining approximately 80% of patients formed the subpopulation of MAGELLAN. MARINER randomized 12,024 patients from 671 sites in 36 countries[9] and the MARINER safety population included 11,962 patients.

Demographics and other baseline characteristics among the three populations (►Table 1) were balanced between treatment groups and generally similar across the three populations except for older age in patients with renal impairment versus those with normal renal function (mean ages were approximately 78 and 67 years, respectively). The reasons for hospitalization were similar except for heart failure which was more common in those with renal impairment (range 47–55%) than in those with normal renal function (range 28–37%). Heart failure and hypertension were the most common medical disorders overall.

Efficacy

In the overall MAGELLAN population, the incidence of the primary efficacy endpoint (asymptomatic proximal DVT, symptomatic VTE, and VTE-related mortality) at day 35 was lower in the rivaroxaban group than in the enoxaparin/placebo group both in patients with impaired renal function (7.18% vs. 9.48%, respectively) and with normal renal function (3.73% vs. 4.64%, respectively) (►Fig. 1A). Compared with enoxaparin/placebo, the RR with rivaroxaban in patients with impaired renal function (RR = 0.77; 95% CI 0.52–1.14) was similar to that in patients with normal renal function (RR = 0.80; 95% CI 0.61–1.06) in the MAGELLAN population and the MAGELLAN subpopulation (►Fig 1A).

In patients with renal impairment, the incidences of symptomatic VTE and VTE-related death with rivaroxaban and enoxaparin/placebo were 1.54 and 2.49%, respectively, in MAGELLAN and 1.41 and 2.27%, respectively, in the MAGELLAN subpopulation. In those with normal renal function, the incidences of symptomatic VTE and VTE-related death with rivaroxaban and enoxaparin/placebo were 0.92 and 1.11%, respectively, in MAGELLAN and 0.81 and 1.06%, respectively, in the MAGELLAN subpopulation (►Fig. 1B).

By contrast, the incidences of the composite of symptomatic VTE and VTE-related death at 45 days in patients with renal impairment were 1.64% with both rivaroxaban (7.5 mg once daily) and placebo in the MARINER study (►Fig 1B, left

Table 1 Demographics and clinical characteristics by renal function

CrCl 30 ≤ 50 mL/min						
	MAGELLAN		MAGELLAN subpopulation		MARINER	
	Rivaroxaban 10 mg QD N = 780 n (%)	Enoxaparin/ placebo N = 804 n (%)	Rivaroxaban 10 mg QD N = 637 n (%)	Enoxaparin/ placebo N = 662 n (%)	Rivaroxaban 7.5 mg QD N = 1,092 n (%)	Placebo N = 1,091 n (%)
Age, mean ± SD, y	78.6 ± 8.0	78.2 ± 8.5	78.8 ± 7.9	78.5 ± 8.3	78.1 ± 7.6	78.6 ± 7.9
< 65 y	45 (5.8)	65 (8.1)	31 (4.9)	49 (7.4)	67 (6.1)	62 (5.7)
65 to < 75 y	151 (19.4)	141 (17.5)	119 (18.7)	108 (16.3)	208 (19.1)	206 (18.9)
≥ 75 y	584 (74.9)	598 (74.4)	487 (76.5)	505 (76.3)	817 (74.8)	823 (75.4)
Sex, male	366 (46.9)	344 (42.8)	285 (44.7)	275 (41.5)	411 (37.6)	417 (38.2)
Reason of hospitalization						
Heart failure	367 (47.1)	372 (46.3)	308 (48.4)	320 (48.3)	598 (54.8)	577 (52.9)
Acute ischemic stroke	97 (12.4)	102 (12.7)	83 (13.0)	92 (13.9)	99 (9.1)	94 (8.6)
Acute infectious and inflammatory diseases	350 (44.9)	350 (43.5)	298 (46.8)	292 (44.1)	NA	NA
Acute infectious disease	330 (42.3)	335 (41.7)	285 (44.7)	279 (42.1)	166 (15.2)	175 (16.0)
Acute inflammatory rheumatic disease	33 (4.2)	23 (2.9)	26 (4.1)	21 (3.2)	11 (1.0)	8 (0.7)
Acute respiratory insufficiency	214 (27.4)	229 (28.5)	179 (28.1)	192 (29.0)	217 (19.9)	237 (21.7)
Comorbidities						
Atrial fibrillation	184 (23.6)	157 (19.5)	151 (23.7)	140 (21.2)	57 (5.2)	65 (6.0)
COPD	251 (32.1)	254 (31.6)	208 (32.7)	212 (32.0)	317 (29.0)	339 (31.1)
Coronary artery disease	193 (24.7)	187 (23.3)	156 (24.5)	141 (21.3)	210 (19.2)	211 (19.3)
Diabetes	254 (32.6)	234 (29.1)	213 (33.4)	186 (28.1)	29 (27.0)	306 (28.1)
Heart failure	410 (52.6)	408 (50.8)	346 (54.3)	354 (53.5)	677 (62.0)	650 (59.6)
Hypertension	604 (77.4)	627 (78.0)	500 (78.5)	521 (78.7)	887 (81.2)	882 (80.8)
Kidney dysfunction	276 (35.4)	266 (33.1)	223 (35.0)	210 (31.7)	125 (11.5)	121 (11.1)
Myocardial infarction	249 (31.9)	242 (30.1)	192 (30.1)	197 (29.8)	347 (31.8)	357 (32.7)
D-dimer > 2× ULN	441 (56.5)	469 (58.3)	357 (56.0)	386 (58.3)	847 (77.6)	858 (78.6)
History of cancer	117 (15.0)	119 (14.8)	71 (11.1)	70 (10.6)	96 (8.8)	101 (9.3)
History of VTE	39 (5.0)	42 (5.2)	33 (5.2)	42 (6.3)	100 (9.2)	86 (7.9)
CrCl ≥ 50 mL/min						
	MAGELLAN		MAGELLAN subpopulation		MARINER	
	Rivaroxaban 10 mg QD N = 3,058 n (%)	Enoxaparin/ placebo N = 3,058 n (%)	Rivaroxaban 10 mg QD N = 2,456 n (%)	Enoxaparin/ placebo N = 2,462 n (%)	Rivaroxaban 10 mg QD N = 4,890 n (%)	Placebo N = 4,889 n (%)
Age, mean ± SD, y	66.5 ± 11.3	66.6 ± 11.2	66.8 ± 11.4	66.9 ± 11.1	67.8 ± 9.6	67.7 ± 9.6
< 65 y	1,250 (40.88)	1,274 (41.66)	980 (39.90)	998 (40.5)	1,736 (35.5)	1,776 (36.3)
65 to < 75 y	965 (31.56)	921 (30.12)	766 (31.19)	740 (30.1)	1,826 (37.3)	1,811 (37.0)
≥ 75 y	843 (27.57)	863 (28.22)	710 (28.91)	724 (29.4)	1,328 (27.2)	1,302 (26.6)
Sex, male	1,788 (58.5)	1,700 (55.6)	1,404 (57.2)	1,345 (54.6)	2,705 (55.3)	2,725 (55.7)
Reason of hospitalization						
Heart failure	862 (28.2)	881 (28.8)	745 (30.3)	771 (31.3)	1,834 (37.5)	1,812 (37.1)
Acute ischemic stroke	574 (18.8)	574 (18.8)	485 (19.7)	480 (19.5)	759 (15.5)	769 (15.7)

Table 1 (*Continued*)

Acute infectious and inflammatory diseases	1,473 (48.2)	1,451 (47.4)	1,266 (51.5)	1,249 (50.7)	NA	NA
Acute infectious disease	1,416 (46.3)	1,394 (45.6)	1,212 (49.3)	1,203 (48.9)	875 (17.9)	857 (17.5)
Acute inflammatory rheumatic disease	115 (3.8)	121 (4.0)	104 (4.2)	102 (4.1)	74 (1.5)	82 (1.7)
Acute respiratory insufficiency	817 (26.7)	880 (28.8)	693 (28.2)	725 (29.4)	1,346 (27.5)	1,369 (28)
Comorbidities						
Atrial fibrillation	361 (11.8)	326 (10.7)	309 (12.6)	283 (11.5)	146 (3.0)	147 (3.0)
COPD	952 (31.1)	937 (30.6)	787 (32.0)	777 (31.6)	1,687 (34.5)	1,741 (35.6)
Coronary artery disease	506 (16.6)	531 (17.4)	400 (16.3)	418 (17.0)	745 (15.2)	742 (15.2)
Diabetes	976 (31.9)	933 (30.5)	792 (32.3)	772 (31.4)	1,447 (29.6)	1,368 (28.0)
Heart failure	999 (32.7)	1,028 (33.6)	861 (35.1)	892 (36.2)	2,187 (44.7)	2,182 (44.6)
Hypertension	2,050 (67.0)	2,027 (66.3)	1,711 (69.7)	1,685 (68.4)	3,825 (78.2)	3,856 (78.9)
Kidney dysfunction	384 (12.6)	374 (12.2)	293 (11.9)	305 (12.4)	287 (5.9)	254 (5.2)
Myocardial infarction	623 (20.4)	642 (21.0)	490 (20.0)	520 (21.1)	1,177 (24.1)	1,149 (23.5)
D-dimer $> 2\times$ ULN	1,261 (41.2)	1,293 (42.3)	1,005 (40.9)	1,023 (41.6)	3,365 (68.8)	3,362 (68.8)
History of cancer	548 (17.9)	525 (17.2)	269 (11.0)	248 (10.1)	387 (7.9)	428 (8.8)
History of VTE	149 (4.9)	126 (4.1)	124 (5.0)	102 (4.1)	665 (13.6)	658 (13.5)

Abbreviations: COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; SD, standard deviation; ULN, upper limit of normal; VTE, venous thromboembolism.

panel), whereas in patients with normal renal function in the MARINER study, the incidences of symptomatic VTE and VTE-related death were 0.65 and 0.98% with rivaroxaban (10 mg once daily) and placebo, respectively (►**Fig. 1B**, right panel). Taken together, these data suggest that the 10 mg once daily dose of rivaroxaban reduces the risk of VTE in patients with impaired renal function to a similar extent as it does in patients with normal renal function, whereas the 7.5 mg once daily dose of rivaroxaban is ineffective in patients with renal impairment.

Safety

In MAGELLAN overall, the incidence of major bleeding with rivaroxaban and enoxaparin/placebo up to day 35 were 1.08 and 0.38%, respectively. The incidence of major bleeding (►**Fig. 2A**) in patients with renal impairment was higher than that in those with normal renal function in the rivaroxaban group (1.54 and 0.98%, respectively), but not in the enoxaparin/placebo group (0.37 and 0.39%, respectively). The incidence of major bleeding was lower in the MAGELLAN subpopulation than in the overall MAGELLAN population regardless of renal function. Within the subpopulation treated with rivaroxaban, the incidence of major bleeding was 0.94% in patients with renal impairment and 0.61% in those with normal renal function. In the enoxaparin/placebo arm, the incidence of major bleeding in patients with renal impairment was similar to that in patients with normal renal function (0.45 and 0.49%, respectively). The incidence of clinically relevant bleeding with rivaroxaban and enoxaparin/placebo in the MAGELLAN subpopulation was similar to that in the overall MAGELLAN. However, the incidence of

clinically relevant bleeding in the MAGELLAN subpopulation was still higher with rivaroxaban than with enoxaparin/placebo (4.71% vs. 2.12% in patients with renal impairment and 3.14% vs. 1.38% in patients with normal renal function) (►**Fig. 2B**).

In MARINER, which prospectively applied five exclusion criteria that were retrospectively used to create the MAGELLAN subpopulation, the overall incidence of major bleeding with rivaroxaban was lower than that in MAGELLAN overall (0.28 and 1.1%, respectively). When these criteria were applied to create the MAGELLAN subpopulation, the incidence of major bleeding decreased from 1.1 to 0.61% in those with normal renal function and to 0.94% in those with impaired renal function (►**Fig. 2A**). The incidence of bleeding with rivaroxaban 7.5 mg, which was administered to patients with renal impairment, was similar to that with the 10 mg dose (0.37 and 0.27%, respectively) (►**Fig. 2A**). Therefore, applying the criteria used in MARINER to exclude patients at high risk of bleeding appears to reduce the potential bleeding liability with the 10 mg dose of rivaroxaban in patients with normal and impaired renal function.

Rivaroxaban Exposures

In the MARINER trial, the plasma concentration of rivaroxaban was measured in 72 and 245 patients in the 7.5 mg and 10 mg dose groups, respectively. Dose reduction from 10 mg to 7.5 mg in patients with renal impairment resulted in rivaroxaban plasma concentrations largely overlapping with those found with the 10 mg dose in patients with normal renal function. ►**Fig. 3** shows the geometric means and 95% CI for the plasma rivaroxaban concentration time curves for days 7
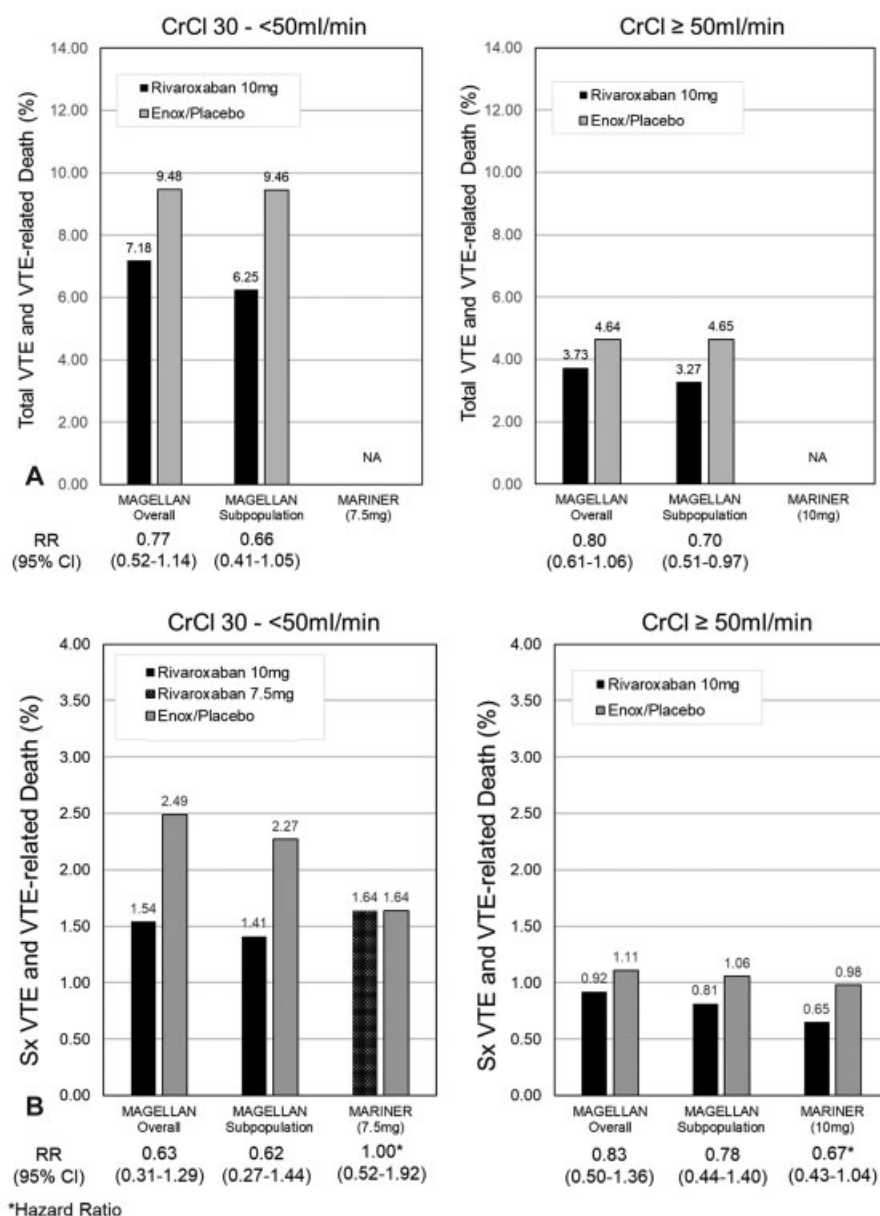
Fig. 1 (**A**, **B**) Key efficacy outcomes by renal function. (**A**) Total venous thromboembolism (VTE) (asymptomatic proximal deep vein thrombosis [DVT] and symptomatic VTE) and VTE-related death (%).(**B**) Symptomatic VTE and VTE-related death (%).

and 21 with the 7.5 mg dose as a percentage of those found with the 10 mg dose. ►**Table 2** shows the steady-state rivaroxaban exposures in patients with or without renal impairment in the MARINER and MAGELLAN trials. In MAGELLAN, the geometric mean of AUCss with the 10 mg dose of rivaroxaban was 12.2% higher in patients with renal impairment than in those with normal renal function (2108.1 and1878.6 μg*h/L, respectively). In MARINER, the geometric mean of AUCss for rivaroxaban was 9.4% lower with the 7.5 mg rivaroxaban dose in patients with renal impairment than with the 10 mg rivaroxaban dose in patients with normal renal function (1903.8 and 2100.6 μg*h/L, respectively). Taken together with the safety and efficacy data, these findings suggest that although the 7.5 mg dose in patients with renal impairment provides exposure similar to that in patients with normal renal function, it does not reduce the risk of VTE.

Therefore, rivaroxaban concentrations higher than those achieved with the 7.5 mg dose are needed to maintain efficacy in patients with impaired renal function.

Discussion

The results of this study reveal that (1) acutely ill medical patients with renal impairment are at higher risk for VTE and bleeding than those with normal renal function, (2) compared with placebo, the use of a 7.5 mg once daily dose of rivaroxaban in medically ill patients with renal impairment not only fails to reduce the risk of VTE, but increases the risk of bleeding to the same extent as the 10 mg once daily dose of rivaroxaban in patients with normal renal function likely because the plasma rivaroxaban concentrations with the two doses are comparable, (3) a higher rivaroxaban exposure
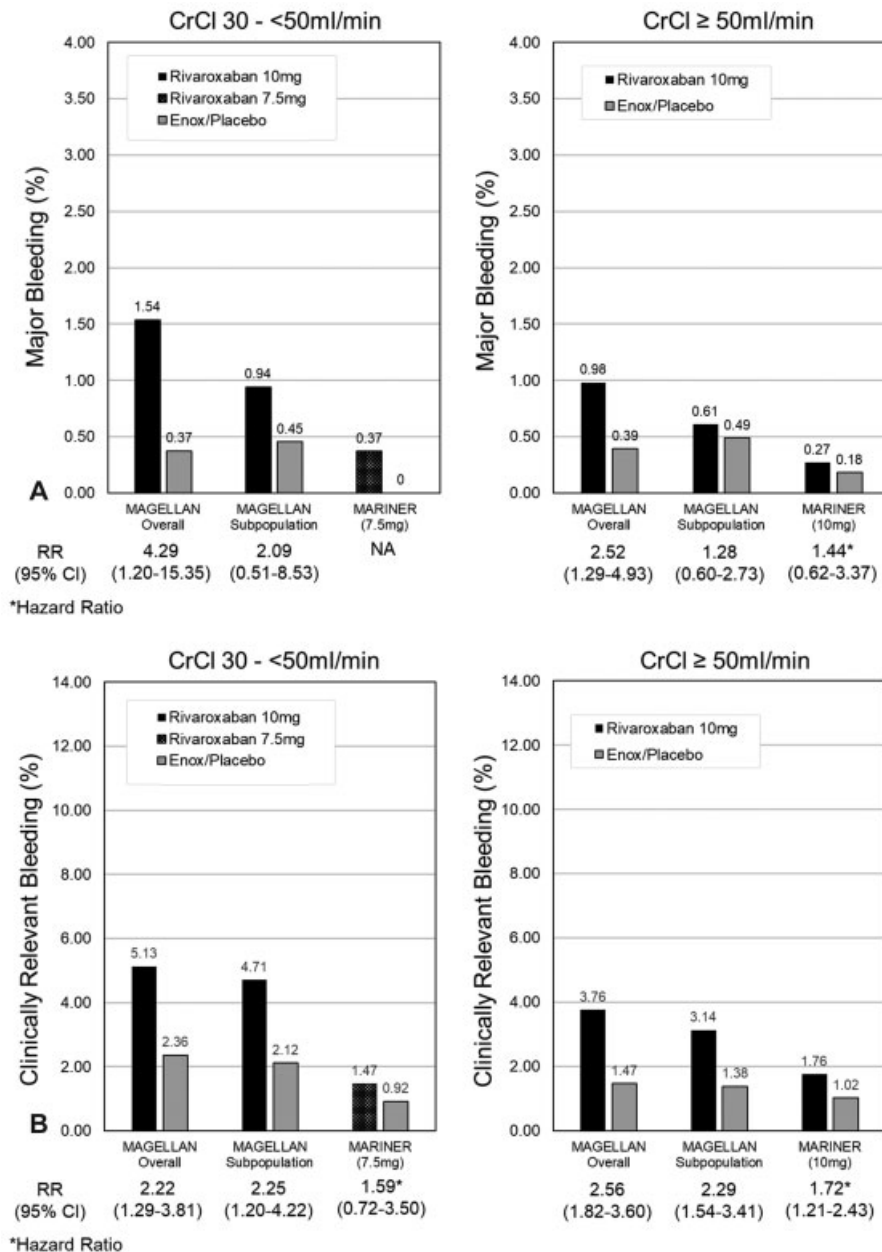
Fig. 2 (**A**, **B**) Key safety outcomes by renal function. (**A**) Major bleeding (%). (**B**) Clinically relevant bleeding, the composite of major and clinically relevant nonmajor bleeding (%).

than that obtained with the 7.5 mg dose is needed to maintain efficacy in patients with impaired renal function, and (4) exclusion of patients at high risk for bleeding using clinical criteria alone appears to enhance the benefit–risk profile of the 10 mg once daily regimen of rivaroxaban for extended thromboprophylaxis in acutely ill medical patients.

The observation that patients with renal impairment are at higher risk for VTE and bleeding than those with normal renal function is in line with previous findings.[20,21] Because of the higher risk of bleeding, guidelines initially recommended either avoiding thromboprophylaxis with anticoagulants that bioaccumulate in such patients or considering a lower dose.[5] Assessing the competing risks of VTE and bleeding in patients with renal impairment is complicated because they tend to be older and have more comorbid

conditions than patients with normal renal function.[18] Therefore, there remains a need for anticoagulant regimens that optimize benefit and risk in medically ill patients with impaired renal function who require thromboprophylaxis.

The five criteria used prospectively in the MARINER trial to exclude patients at risk for bleeding were identified by post hoc analysis of factors associated with major bleeding in the MAGELLAN study. With application of these exclusion criteria, the incidence of major bleeding with rivaroxaban in the MARINER trial was less than 0.4% in patients with or without renal impairment. However, at least two other factors may have contributed to the low incidence of major bleeding in the MARINER trial. First, patients were enrolled at the time of hospital discharge, thereby excluding those who bled while in hospital. Second, the dose of rivaroxaban
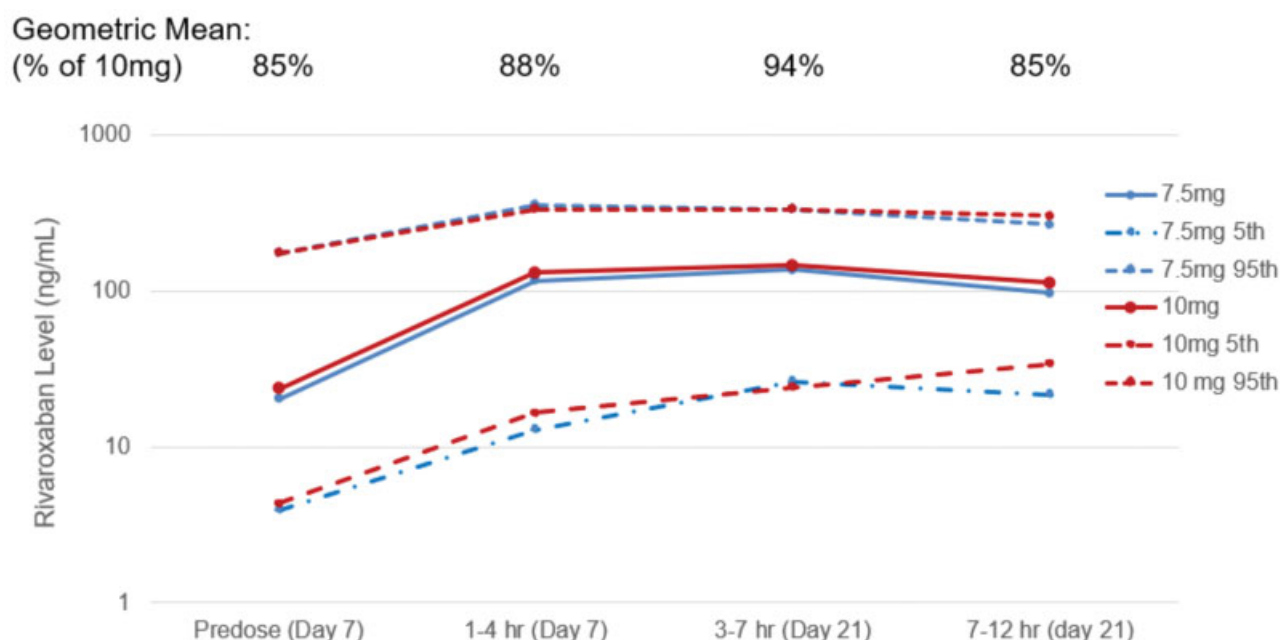
Fig. 3 Geometric mean rivaroxaban concentrations - by dose in the MARINER trial. Geometric mean concentrations (blue solid line with solid circle) of rivaroxaban in patients with a creatinine clearance of 30–<50 mL/min taking the 7.5 mg dose at day 7 (pre- and 1–4 hours postdose) and day 21 (3–7 and 7–12 hours postdose) are also calculated as a percentage of the geometric mean concentrations (red solid line with solid circle) in patients with a creatinine clearance ≥ 50 mL/min taking the 10 mg rivaroxaban dose at the same pharmacokinetic (PK) sampling times. The percentage results are shown on top of the plot. Note that 5th (lower position) and 95th (higher position) percentile concentration of rivaroxaban with the 7.5 mg dose (blue dash line) and with the 10 mg dose (red dash line) are also shown in the plot. For this PK analysis, $N = 72$ for the 7.5 mg dose group, and $N = 245$ for the 10 mg dose group.

was decreased from 10 to 7.5 mg in patients with a creatinine clearance less than 50 mL/min to prevent increased drug exposure. Although this dose reduction strategy reduced the exposure, the 7.5 mg rivaroxaban dose regimen was ineffective because the incidence of symptomatic VTE and VTE-related death with this regimen was nearly identical to that with placebo. The incidence of major bleeding with the 7.5 mg dose of rivaroxaban in patients with renal impairment was higher than that with the 10 mg dose of rivaroxaban in patients with normal renal function (0.37 and 0.27%, respectively). Therefore, the low incidence of major bleeding with rivaroxaban observed in the MARINER trial is more likely to reflect the exclusion of patients at high risk for bleeding using clinical criteria than the dose reduc-

tion strategy used in patients with impaired renal function or the delay in initiation of rivaroxaban until hospital discharge.

A failure of a dose reduction strategy to maintain efficacy in renally impaired patients was seen in the APEX trial with betrixaban.[22] Taken together with the data from this analysis, these findings suggest that dose reduction in medically ill patients with renal impairment is problematic. Therefore, the 10 mg dose of rivaroxaban should be used for thromboprophylaxis in such patients regardless of renal function just like the 20 mg dose of rivaroxaban is used for VTE treatment in patients with normal or impaired renal function.

The importance of excluding patients at high risk for bleeding is highlighted by comparison of the results in the subpopulation of patients in the MAGELLAN trial with those

Table 2 Rivaroxaban exposure in MAGELLAN and MARINER by renal function

Study	Rivaroxaban dose (mg) (no. of subjects)	CrCl (mL/min)	AUCss (µg·h/L) Geometric mean (5–95% percentile)	Cmaxss (µg/L) Geometric mean (5–95% percentile)	Cminss (µg/L) Geometric mean (5–95% percentile)
MAGELLAN	10 OD (6)	≥ 30 to < 50	2108.1 (1082.1–3467.6)	185.6 (128.4–268.6)	20.5 (6.88–84.0)
	10 OD (32)	≥ 50	1878.6 (1054.1–3443.0)	186.5 (127.5–311.6)	13.19 (2.73–66.8)
MARINER	7.5 OD (72)	≥ 30 to < 50	1903.8 (1063.7–4072.5)	162.5 (113.5–248.9)	21.1 (4.1–111.3)
	10 OD (245)	≥ 50	2100.6 (1191.5–4075.1)	185.1 (135.4–258.3)	21.4 (4.8–106.0)

Abbreviations: AUCss, area under the concentration curve over the dose interval at steady state; Cmaxss, maximum concentration at steady state; Cminss, minimum concentration at steady state; CrCl, creatinine clearance; OD, once-daily dose.

in the overall MAGELLAN population. Exclusion of patients with the five risk factors for bleeding in the MAGELLAN subpopulation was associated with a reduction in the incidence of major bleeding from 1.54 to 0.94% in patients with impaired renal function and from 0.98 to 0.61% in those with normal renal function. The comparison of the MAGELLAN, MAGELLAN subpopulation, and MARINER findings suggests that using the five criteria to exclude patients at high risk for bleeding will enhance the safety of the 10 mg dose of rivaroxaban in patients with or without renal impairment.

This study has strengths and limitations. The strengths include the large sample size, the double-blind design of the trials, and the central adjudication of outcome events by committees whose members were unaware of treatment allocation. Limitations include the retrospective application of exclusion criteria used in MARINER to create the MAGELLAN subpopulation. Although the risk factors for bleeding were applied retrospectively, this excluded only about 20% of the patients enrolled in MAGELLAN. Furthermore, the outcomes used in the analyses were the same as those used in the trials to limit bias. The APEX study with betrixaban utilized a similar set of exclusion criteria which also improved the benefit–risk profile in medically ill patients.[22]

In summary, the results of this analysis suggest a favorable benefit–risk profile of the 10 mg once daily dose of rivaroxaban for extended thromboprophylaxis in acutely ill medical patients with impaired or normal renal function. The safety of this regimen can be enhanced without loss of efficacy by excluding patients with key risk factors for bleeding. Additional studies are needed to identify effective and safe methods of thromboprophylaxis for patients at high risk for bleeding.

What is known about this topic?

- Patients with renal impairment are at increased risk of thrombosis and bleeding.
- Acutely ill, medical patients are at increased risk for venous thromboembolism and this can be reduced with extended thromboprophylaxis.

What does this paper add?

- A dose of 10 mg once daily of rivaroxaban provides the best benefit–risk profile for extended thromboprophylaxis in renally impaired patients.
- The safety of rivaroxaban in renally impaired medically ill patients can be improved by avoiding patients with five key risk factors for bleeding.

Authors' Contributions

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

Conflict of Interest
J.I.W.: Bayer, Boehringer Ingelheim, Bristol-Meyers Squibb, Daiichi Sankyo, Ionis, Janssen, Merck, Novartis, Pfizer, Portola; A.C.S.: Janssen Research & Development LLC, Bayer, Portola, Boehringer Ingelheim, ATLAS group: Research Grants and Consulting; C.L., J.X., W.L., E.S., J.A., D. A., E.S.B.: Janssen Research & Development LLC: Employee/Stock; Y.D.S., T.E.S.: Bayer U.S. LLC: Employee; G.E.R.: Janssen Research & Development LLC & Bayer U.S. LLC, Daiichi Sankyo, Portola, Boehringer Ingelheim, PHRI Mc Master, Tetherex, Eli Lilly: Research Grants and Consulting.

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