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Risk of Severe Bleeding With Extended Rivaroxaban to Prevent Venous Thromboembolism in Acute Medically Ill Patients With Bronchiectasis

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Abstract

Background: Bronchiectasis is a chronic inflammation of the bronchi with recurrent infections and hemoptysis. The MAGELLAN study compared oral rivaroxaban, 10 mg once daily (QD), for 35 ± 4 days with subcutaneous enoxaparin 40 mg QD for 10 ± 4 days followed by placebo for 25 ± 4 days to prevent venous thromboembolism in patients hospitalized with an acute medical illness. MAGELLAN included a subset of patients with bronchiectasis. In a post hoc analysis, we evaluated the incidence and severity of pulmonary bleeding in patients with bronchiectasis who were hospitalized for an acute medical illness. This analysis included MAGELLAN patients diagnosed with bronchiectasis at baseline. Patients were evaluated by treatment group for International Society on Thrombosis and Haemostasis major bleeding, non-major clinically relevant (NMCR) bleeding, and the composite of the 2 (ie, clinically relevant bleeding). **Results:** Medically ill patients with bronchiectasis were randomized to rivaroxaban (n = 60) or enoxaparin/placebo (n = 61). There were 2 fatal pulmonary bleeds and 1 fatal gastrointestinal bleed in the rivaroxaban arm and no fatal or major bleeding in the enoxaparin/placebo arm. The incidence of major bleeding was 5% in the rivaroxaban arm. One NMCR bleed occurred in the rivaroxaban arm and 2 NMCR bleeds occurred in the enoxaparin/placebo arm. The incidence of clinically relevant bleeding was 6.7% versus 3.3% in the rivaroxaban and enoxaparin/placebo groups, respectively (relative risk = 2.06 [95% confidence interval: 0.351-12.046]). **Conclusion:** In-patients hospitalized with bronchiectasis and an acute medical illness, clinically relevant bleeding, including fatal pulmonary hemorrhage, occurs more frequently with extended rivaroxaban thromboprophylaxis than with enoxaparin followed by placebo.

Keywords

bronchiectasis, medically ill patients, severe bleeding, thromboprophylaxis

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Introduction

Bronchiectasis is a chronic disease characterized by recurrent infection and inflammation of the bronchial tree.[1,2] In the United States, there are currently over 110 000 people diagnosed with bronchiectasis and the prevalence of bronchiectasis increases with increasing age.[3] The number of patients diagnosed with bronchiectasis has increased in the past 10 years due at least in part to the widespread availability of computed tomography. Recently reported incidence rates range between 566 and 701 per 100 000 person-years.[4,5]

The natural history of bronchiectasis includes chronic symptoms that worsen over time.[6–8] Common symptoms are chronic cough, sputum production, and symptoms of recurrent pulmonary infections, for example, pneumonia. Recurrent minor episodes of hemoptysis often occur in patients with bronchiectasis.[9] Furthermore, patients with bronchiectasis may require hospitalization for an acute medical illness, and they may receive an anticoagulant to reduce the risk of venous thromboembolism (VTE) as a complication of their hospitalization. However, the risk of bleeding when patients with bronchiectasis receive an anticoagulant to prevent VTE is not well described.

Enoxaparin, a low-molecular heparin with antifactor Xa to IIa activities, is administrated subcutaneously for thromboprophylaxis and monitoring of platelet count and renal function.[10] In contrast, rivaroxaban, a Factor Xa inhibitor, has the advantage of being orally administered without dose adjustment or routine coagulation monitoring.[11] MAGELLAN, a multicenter, randomized, double-blind clinical trial, compared the efficacy and safety of oral rivaroxaban administered for an extended period with subcutaneous enoxaparin administered for a standard period, followed by a placebo for an extended period.[12] Patients diagnosed with bronchiectasis who were enrolled in MAGELLAN provided an opportunity to describe the risk of bleeding with extended use of an anticoagulant to prevent VTE. In this post hoc analysis, we evaluated the efficacy and safety of extended thromboprophylaxis with rivaroxaban in MAGELLAN patients with bronchiectasis.

Material and Methods

Data Sharing Statement

At present, the sponsor's policy is to share data after regulatory approval in accordance with the policy of its codevelopment 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 codevelopment partner's section of the portal.

Trial Design

The MAGELLAN study design and results have been reported previously.[12,13] Briefly, MAGELLAN was a multicenter, randomized, double-blind, parallel-group efficacy and safety study comparing oral rivaroxaban (10 mg once daily [QD]) administered for 35 ± 4 days with subcutaneous enoxaparin (40 mg QD) administered for 10 ± 4 days followed by placebo for an additional 25 ± 4 days, for the prevention of VTE in patients hospitalized for an acute medical illness. Randomization was performed in permuted blocks with the use of an interactive voice-response system, with stratification according to center.

Patients

Eligible patients included men and women, aged 40 years or older who were hospitalized for an acute medical illness (ie, heart failure exacerbation, active cancer, acute ischemic stroke, acute infectious and inflammatory disease, and acute respiratory insufficiency), who were at risk of VTE due to immobility and had at least one additional risk factor for VTE such as age ≥75 years, history of cancer, history of VTE, history of heart failure, thrombophilia, acute infectious disease contributing to the hospitalization, or body mass index (BMI) ≥35 kg/m^2. Patients were excluded if they met conditions that may have increased the risk of bleeding, including intracranial hemorrhage such as major surgery, history of known coagulopathy or bleeding diathesis, history of hemorrhagic stroke, intracranial neoplasm, and clinically significant bleeding within 30 days of randomization. Additional exclusion criteria were renal dysfunction and known significant liver disease or liver function tests abnormalities. Treatment with single antiplatelet or dual antiplatelet treatment was allowed. Relevant medical history was collected in all the randomized patients. Bleeding risk factors in medically ill patients (ie, dual antiplatelet therapy, active cancer, bronchiectasis, and gastroduodenal ulcer or bleeding within 3 months from randomization) were previously identified with a post hoc analysis of MAGELLAN[14] and analyzed in the MAGELLAN patients with bronchiectasis and MAGELLAN patients without bronchiectasis in this manuscript. Patients underwent a compression ultrasound examination of the leg veins at Day 10 and Day 35.

This post hoc analysis was performed in the MAGELLAN patients with a clinical diagnosis of bronchiectasis at baseline. Demographics, baseline clinical characteristics, primary efficacy endpoints (ie, composite of asymptomatic deep vein thrombosis [DVT], symptomatic DVT, symptomatic pulmonary embolism [PE], and VTE-related death), and primary safety endpoint (clinically relevant bleeding, the composite of International Society on Thrombosis and Haemostasis [ISTH] major bleeding and non-major clinically relevant [NMCR]

bleeding) from Day 1 to Day 35 were evaluated by treatment arm.

Statistical Analyses

Selected statistical analyses to evaluate efficacy and safety in the MAGELLAN bronchiectasis population were rerun using the original study definition and data rules. In all the results presented here, the relative risk (RR) for the primary efficacy endpoint was calculated to evaluate the superiority of rivaroxaban over enoxaparin/placebo in a modified Intention-to-Treat (mITT) population at Day 35, and the RR for the principal safety endpoint was provided in the safety population. The 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method with stratification according to geographic region. The mITT Day 35 population included patients who were valid for the safety analysis with an adequate ultrasonography assessment of VTE at Day 35. The efficacy events were assessed by an independent Ultrasonography Adjudication Committee and the Clinical Events Adjudication Committee. Major bleeding, defined by ISTH criteria, was the primary bleeding endpoint in this analysis and was assessed in the safety population consisting of the on-treatment period plus 2 days. Results, RRs, including their corresponding CIs, were calculated using the Mantel-Haenszel method available in PROC FREQ of SAS version 9.[15]

Results

Demographics and Baseline Characteristics

Acute medically ill patients (n = 8101) from 562 sites in 52 countries were randomized in the MAGELLAN study with 7998 patients included in the safety population as they received at least one dose of study medication.[12] The MAGELLAN bronchiectasis population consisted of 121 patients in the safety population with 60 patients randomized to rivaroxaban and 61 patients to enoxaparin/placebo.

There were no major differences for age, sex, or geographic region in the bronchiectasis population when compared with the population without bronchiectasis (Table 1).

The bronchiectasis subpopulation differed from the population without bronchiectasis with respect to relevant medical history, reason for hospitalization, VTE risk, and bleeding risk.

Medical history of tuberculosis, exacerbations of chronic obstructive pulmonary disease (COPD), asthma, and/or infectious diseases were higher in the bronchiectasis population (25.6%, 54.5%, 24.8%, and 82.6%) compared to the MAGELLAN population without bronchiectasis (2.9%, 26%, 7.2%, and 44.8%). Fewer patients with the admitting diagnosis of heart failure and more patients with hospitalization for infectious diseases were enrolled in the bronchiectasis population (18.2% vs 32.6% and 82.6% vs 44.8%, respectively). More than 1 admitting diagnosis was more common in the bronchiectasis population than in those without bronchiectasis (68.6% vs 30.1%, respectively), and in most cases, an infectious disease was one of the admitting diagnoses for patients with bronchiectasis (Table 1).

There were differences in the incidence of VTE and bleeding risk factors in the bronchiectasis population versus the MAGELLAN population without bronchiectasis (Table 1). The incidence of an acute infectious disease contributing to hospitalization was higher in the bronchiectasis group (44.6% vs 13.9%), while the incidence of other VTE factors such as BMI $\geq$35 kg/m^2 (5.0% vs 15.4%), chronic venous insufficiency (9.9% vs 14.9%), severe varicosis (7.4% vs 12.0%), and history of cancer (12.4% vs 17.0%) was lower in the bronchiectasis population compared to the MAGELLAN population without bronchiectasis. Among the bleeding risk factors, patients with bronchiectasis were more likely to report bleeding within 3 months before randomization compared to the MAGELLAN population without bronchiectasis (6.6% vs 3.2%) and less likely to report the use of dual antiplatelet therapy at baseline (1.7% vs 6.1%).

Efficacy

At Day 35 or at the end of the treatment phase of the study, the incidence of total VTE (composite of asymptomatic proximal DVT, symptomatic DVT, symptomatic PE, and VTE-related death) in the bronchiectasis population was numerically higher in the rivaroxaban arm (11.6% [5/43]) than in the enoxaparin/placebo arm (4.2% [2/48]) with an RR of 2.36 (95% CI: 0.48-11.55). In the MAGELLAN population without bronchiectasis, the incidence of total VTE at Day 35 or at the end of the treatment phase of the study was significantly lower in the rivaroxaban treatment arm than in the enoxaparin/placebo treatment arm, 4.3% (126/2924) versus 5.8% (173/3009), respectively, with an RR of 0.75 (95% CI: 0.60-0.94).

In the bronchiectasis population, the incidence of asymptomatic DVT at Day 35 was numerically higher in the rivaroxaban treatment arm (9.3% [4/43]) than in the enoxaparin/placebo treatment arm (2.1% [1/48]) with an RR of 3.71 (95% CI: 0.40-34.05). In the MAGELLAN population without bronchiectasis, the Day 35 incidence of asymptomatic DVT was 3.4% (99/2924) in participants treated with rivaroxaban and 4.4% (132/3009) in participants treated with enoxaparin/placebo with an RR of 0.77 (95% CI: 0.60-1.00) (Table 2).

Safety

The incidence of major bleeding was significantly higher in the bronchiectasis population in comparison to the MAGELLAN population without bronchiectasis. In patients with bronchiectasis, the incidence of major bleeding was 5% (3/60) in the rivaroxaban treatment arm and 0 in the enoxaparin/placebo treatment arm (Table 3). In the MAGELLAN population without bronchiectasis, the incidence of major bleeding at the end of the study was 1.0% (40/3937) in the rivaroxaban treatment arm and 0.4% (15/3940) in the enoxaparin-placebo arm (RR = 2.67, 95% CI: 1.48-4.82). In the subgroup of patients with bronchiectasis, there were 3 fatal bleeding events (2

Table 1. Demographics and Baseline Characteristics (Safety Analysis Set).

Characteristic	Patients with bronchiectasis			Patients without bronchiectasis			*P* value
	Rivaroxaban N = 60, n (%)	Enoxaparin/placebo N = 61, n (%)	Total N = 121, n (%)	Rivaroxaban N = 3937, n (%)	Enoxaparin/placebo N = 3940, n (%)	Total N = 7877, n (%)	
Age, mean ± SD (years)	69.3 ± 13.1	70.7 ± 12.0	70.0 ± 12.51	69.2 ± 11.8	69.2 ± 11.7	69.2 ± 11.8	.493
Male, sex (%)	34 (56.7)	30 (49.2)	64 (52.9)	2189 (55.6)	2073 (52.6)	4262 (54.1)	.7902
Creatinine clearance							.1461
30 ≤ 50 mL/min	16 (27.1)	14 (24.6)	30 (25.9)	764 (19.8)	790 (20.4)	1554 (20.1)	
50-80 mL/min	16 (27.1)	21 (36.8)	37 (31.9)	1471 (38.1)	1515 (39.2)	2986 (38.6)	
>80 mL/min	26 (44.1)	21 (36.8)	47 (36.8)	1545 (40.0)	1501 (38.8)	3046 (39.4)	
Relevant medical history							
COPD	36 (60)	30 (49.2)	66 (54.5)	1024 (26.0)	1019 (25.9)	2043 (25.9)	<.0001
Asthma	16 (26.7)	14 (23.0)	30 (24.8)	284 (7.2)	286 (7.3)	570 (7.2)	<.0001
Acute respiratory failure	8 (13.3)	9 (14.8)	17 (14.0)	220 (5.6)	237 (6.0)	457 (5.8)	.0001
Respiratory failure	10 (16.7)	8 (13.1)	18 (14.9)	214 (5.4)	202 (5.1)	416 (5.3)	<.0001
Tuberculosis	18 (30.0)	13 (21.3)	31 (25.6)	115 (2.9)	115 (2.9)	230 (2.9)	<.0001
Reason for hospitalization							
Infectious disease	51 (85.0)	49 (80.3)	100 (82.6)	1775 (45.1)	1752 (44.5)	3527 (44.8)	<.0001
Heart failure	13 (21.7)	9 (14.8)	22 (18.2)	1279 (32.5)	1292 (32.8)	2571 (32.6)	.0007
Respiratory insufficiency	44 (73.3)	46 (75.4)	90 (74.4)	1041 (26.4)	1105 (28.0)	2146 (27.2)	<.0001
Ischemic stroke	0	1 (1.6)	1 (0.8)	691 (17.6)	691 (17.5)	1382 (17.5)	<.0001
Active cancer	0	1 (1.6)	1 (0.8)	294 (7.5)	289 (7.3)	583 (7.4)	.0058
Inflammatory rheumatic disease	1 (1.7)	1 (1.6)	2 (1.7)	149 (3.8)	148 (3.8)	297 (3.8)	.2230
More than 1 diagnosis	41 (68.3)	42 (68.9)	83 (68.6)	1167 (29.6)	1203 (30.5)	2370 (30.1)	<.0001
VTE risk factors							
Acute infectious disease contributing to hospitalization	28 (46.7)	26 (42.6)	54 (44.6)	530 (13.5)	568 (14.4)	1098 (13.9)	<.0001
Age ≥75 years	24 (40.0)	26 (42.6)	50 (41.3)	1506 (38.3)	1522 (38.6)	3028 (38.4)	.5180
History of heart failure	21 (35.0)	18 (29.5)	39 (32.2)	1370 (34.8)	1352 (34.3)	2722 (34.6)	.5935
History of cancer	5 (8.3)	10 (16.4)	15 (12.4)	685 (17.4)	656 (16.6)	1341 (17.0)	.1782
Chronic venous insufficiency	7 (11.7)	5 (8.2)	12 (9.9)	605 (15.4)	566 (14.4)	1171 (14.9)	.1281
Severe varicosis	6 (10.0)	3 (4.9)	9 (7.4)	488 (12.4)	456 (11.6)	944 (12.0)	.1255
History of DVT or PE	4 (6.7)	2 (3.3)	6 (5.0)	192 (4.9)	176 (4.5)	368 (4.7)	.8821
BMI ≥35 kg/m^2	3 (5.0)	3 (4.9)	6 (5.0)	601 (15.3)	609 (15.5)	1210 (15.4)	.0016
Bleeding risk factors							
Active cancer reason for hospitalization	0	1 (1.6)	1 (0.8)	294 (7.5)	289 (7.3)	583 (7.4)	.0058
Bleeding within 3 months	3 (5.0)	5 (8.2)	8 (6.6)	123 (3.1)	128 (3.2)	251 (3.2)	.0347
Active gastroduodenal ulcer within 3 months	1 (1.7)	2 (3.3)	3 (2.5)	115 (2.9)	114 (2.9)	229 (2.9)	.7808
Use of dual antiplatelet at baseline	1 (1.7)	1 (1.6)	2 (1.7)	245 (6.2)	232 (5.9)	477 (6.1)	.0428

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

pulmonary, 1 gastrointestinal) in the rivaroxaban arm. These events occurred within the first 10 days of the study while patients were hospitalized and received either rivaroxaban or enoxaparin. COPD was reported in the medical history of all 3 patients with major bleeding with a fatal outcome. In addition, one of these 3 patients had tuberculosis and one had pneumonia (Table 4). In the bronchiectasis population, there was 1 NMCR bleed in the rivaroxaban treatment arm (1.7% [1/60]), and there were 2 NMCR bleeds in the enoxaparin/placebo treatment arm (3.3% [2/61]) (RR = 0.58, 95% CI: 0.06-6.10) (Table 3). In the bronchiectasis population, the incidence of clinically relevant bleeding at Day 35 was 6.7% (4/60) versus 3.3% (2/61) in the rivaroxaban and enoxaparin/placebo groups, respectively (RR = 2.06, 95% CI: 0.35-12.05) (Table 3). In MAGELLAN population without bronchiectasis, there were more NMCR bleeding events in the rivaroxaban treatment arm (3.1% [123/3937]) compared to the enoxaparin/placebo treatment arm (1.3% [50/3940]) (RR = 2.47, 95% CI: 1.78-3.42) (Table 3). The incidence of clinically relevant bleeding at Day 35 in the MAGELLAN population without bronchiectasis was 4.1% (160/3937) versus 1.7% (65/3940) in the rivaroxaban and enoxaparin/placebo groups, respectively (RR = 2.47, 95% CI: 1.86-3.28) (Table 3).

Discussion

The key finding of this post hoc analysis of a large multicenter prospective randomized double-blinded clinical trial is that, in patients with bronchiectasis who were hospitalized for an acute medical illness, thromboprophylaxis with rivaroxaban did not have a favorable benefit-risk profile. In these patients, thromboprophylaxis with rivaroxaban had lower efficacy in preventing VTE and a higher incidence of severe bleeding than standard dose enoxaparin followed by placebo. Patients with bronchiectasis who received rivaroxaban were more likely to experience major bleeding, including fatal pulmonary hemorrhage, than patients with bronchiectasis who received enoxaparin followed by placebo at the time of hospital discharge.

Bronchiectasis is a medical condition characterized by chronic damage of the bronchial walls. In some exacerbations, bleeding can occur spontaneously because of local or diffuse damage of blood vessels supplying the lung.[16] The results of our analysis suggest that the bleeding risk is increased when patients with bronchiectasis are hospitalized with an acute medical illness. All 3 fatal bleeding events observed in this analysis were in patients with bronchiectasis who were hospitalized for an acute exacerbation of COPD.[17] In addition, the 2 fatal pulmonary bleeds occurred in patients with the additional diagnosis of acute respiratory insufficiency and the fatal gastrointestinal bleeding followed by hemorrhagic shock was in a patient with the concomitant diagnosis of severe hospital-acquired pneumonia. The coexistence of pulmonary infections in patients who were hospitalized with bronchiectasis may have contributed to the increased incidence of severe bleeds after receiving rivaroxaban.

Bronchiectasis often complicates a pulmonary infection and affects patients of all ages, with it being most common in the elderly patients, as the prevalence increases with age.[3,18,19] Although there are many comorbidities associated with bronchiectasis, COPD is the most frequent, as there is a large degree of overlap in these diseases.[20] Patients with preexisting COPD and asthma have been found more susceptible to the risk of severe COVID-19, a current pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[21] Our observations suggest that patients with underlying bronchiectasis are also potentially more prone to severe pulmonary bleeding if given prophylactic rivaroxaban for a SARS-CoV-2 pulmonary infection. In addition, COVID-19 survivors even if not hospitalized are at high risk of developing long-term complications including respiratory conditions such as bronchiectasis.[22] Consequently, the prevalence of bronchiectasis is expected to increase and become an important global health burden for COVID-19 survivors.

Patients in the MAGELLAN bronchiectasis population had a high incidence of concomitant acute exacerbation of COPD, as well as a high incidence of hospitalization for infectious diseases. In the MAGELLAN bronchiectasis population, most of the patients had more than 1 (68.6%) admitting diagnosis and many of these diagnoses were acute infectious diseases (82.6%), suggesting the possibility that more than one infectious disease was contributing to the adverse outcomes in patients with bronchiectasis. These patients were functionally debilitated and prone to additional harm as shown by a decreased BMI that has been linked to decreased pulmonary function.[23]

MAGELLAN demonstrated that rivaroxaban prevents VTE in patients hospitalized with an acute medical illness; however, there was an increased risk of bleeding including fatal bleeding.[13] In the MAGELLAN bronchiectasis population, a 50-fold increase in severe bleeding with fatal outcome was observed in the rivaroxaban treatment group compared with the MAGELLAN population without bronchiectasis (5% vs 0.1%, respectively). The narratives of these deaths report that these patients with severe bleeding died when they were still in the hospital after approximately 7 days of rivaroxaban dosing and that death occurred within a very short time from the onset of the bleeding. In a retrospective study of 1804 patients with bronchiectasis in Southwestern China, the prevalence of massive hemoptysis was 7.1% and the identified relevant risk factors for hemoptysis were current smoking and a history of tuberculosis.[24] It was not reported if these patients were taking any anticoagulant or were hospitalized, but the high risk of severe bleeding was comparable to the risk observed in the MAGELLAN bronchiectasis population after taking rivaroxaban. We observed that a percentage of the MAGELLAN population with bronchiectasis had tuberculosis (9.9%) but it remains unknown if any other infectious disease, comorbidities, or lifestyle factors contributed to an increased risk of bleeding in patients with bronchiectasis. Most importantly, among the bleeding risk factors, a history of bleeding within 3 months prior to randomization was a risk

Table 2. Key Efficacy Results at Day 35 (mITT Analysis Set).

Category	Patients with bronchiectasis			Patients without bronchiectasis		
	Rivaroxaban N = 43, n (%)	Enoxaparin/Placebo N = 48, n (%)	Relative risk (95% CI)	Rivaroxaban N = 2924, n (%)	Enoxaparin/placebo N = 3009, n (%)	Relative risk (95% CI)
Total VTE	5 (11.6)	2 (4.2)	2.36 (0.48-11.55)	126 (4.3)	173 (5.8)	0.75 (0.60-0.94)
Asymptomatic DVT	4 (9.3)	1 (2.1)	3.71 (0.40-34.05)	99 (3.4)	132 (4.4)	0.77 (0.60-1.00)
Symptomatic DVT	0	0	NA	13 (0.4)	15 (0.5)	0.90 (0.43-1.88)
Symptomatic PE	0	1 (2.1)	NA	10 (0.3)	13 (0.4)	0.78 (0.34-1.79)
VTE-related Death	1 (2.3)	0	NA	18 (0.6)	30 (1.0)	0.62 (0.34-1.10)

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; mITT, modified intent-to-treat population; PE, pulmonary embolism; VTE, venous thromboembolism; Total VTE, composite of asymptomatic DVT, symptomatic DVT, symptomatic PE and VTE-related death.
Day 35 includes the in-hospital and the post-hospital discharge period.

Table 3. Key Safety Results at Day 35 (Safety Analysis Set).

Category	Patients with bronchiectasis			Patients without bronchiectasis		
	Rivaroxaban N = 60, n (%)	Enoxaparin/placebo N = 61, n (%)	Relative risk (95% CI)	Rivaroxaban N = 3937, n (%)	Enoxaparin/placebo N = 3940, n (%)	Relative risk (95% CI)
Treatment emergent major bleeding	3 (5.0)	0	NA	40 (1.0)	15 (0.4)	2.67 (1.48-4.82)
A fall in hemoglobin ≥2 g/dL	1 (1.7)	0	NA	30 (0.8)	10 (0.3)	3.00 (1.47-6.12)
A transfusion ≥2 units of blood	1 (1.7)	0	NA	23 (0.6)	8 (0.2)	2.87 (1.29-6.41)
At a critical site	0	0	NA	9 (0.2)	4 (0.1)	2.25 (0.70-7.32)
Fatal	3 (5.0)	0	NA	4 (0.1)	1 (<0.1)	3.99 (0.45-35.54)
Nonmajor clinically relevant bleeding	1 (1.7)	2 (3.3)	0.58 (0.06-6.10)	123 (3.1)	50 (1.3)	2.47 (1.78-3.42)
Clinically relevant bleeding	4 (6.7)	2 (3.3)	2.06 (0.35-12.05)	160 (4.1)	65 (1.7)	2.47 (1.86-3.28)

Abbreviation: CI, confidence interval.
Day 35 includes the in-hospital and the post-hospital discharge period.

Table 4. Bleeding in Patients With Bronchiectasis.

Study drug	Duration of study drug	Death study day	Age/sex	Relevant medical history	ISTH classification, site, outcome
Rivaroxaban 10 mg QD	D2	D3	62, Male	Bronchiectasis, COPD, septicemia, tuberculosis	MB, Pulmonary Fatal
	D5	D6	79, Male	Bronchiectasis, COPD, pneumonia	MB, Gastrointestinal Fatal
	D8	D9	52, Male	Bronchiectasis, COPD, hemoptysis, HF, kidney injury	MB, Pulmonary Fatal
	D29	NA	73, Male	Bronchiectasis, COPD, pneumonia, CAD	NMCR, Subcutaneous hematoma in inner right arm Resolved
Enoxaparin 40 mg QD/ Placebo	D22	NA	81, Male	Bronchiectasis, COPD, hypertension, UTI	NMCR, Hematochezia Resolved
	D28[a]	NA	67, Female	Bronchiectasis, pneumonia, hypertension, UTI, recurrent epistaxis	NMCR, Bruise on the knee Resolved

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; ISTH, International Society on Thrombosis and Haemostasis; MB, major bleeding; NMCR, non-major clinically relevant bleeding; QD, once daily; UTI, urinary tract infection.
aOff-treatment.

factor associated with a higher incidence in the MAGELLAN patients with bronchiectasis compared to the MAGELLAN population without bronchiectasis.

The MAGELLAN study overall met its primary endpoint, reducing the incidence of VTE events with extended treatment with rivaroxaban compared with standard dose enoxaparin with an RR of 0.77 (95% CI: 0.62-0.96), see Table 2. In the bronchiectasis population, rivaroxaban did not show a benefit compared with enoxaparin/placebo (RR: 2.36, 95% CI: 0.48-11.55) although the sample size is very small. Nevertheless, considering the high risk of severe bleeding, it appears clear that the benefit-risk balance is unfavorable for rivaroxaban compared to enoxaparin in hospitalized and to placebo in post-hospitalized, medically ill patients with bronchiectasis.

This post hoc analysis has certain limitations. It was based on an observation of increased bleeding in patients with bronchiectasis. The use of antiplatelet therapy has potentially affected the risk of bleeding in these patients. Baseline bronchiectasis was identified by history only and did not require diagnostic confirmation. There was also no report of the anatomical type of bronchiectasis (ie, cylindrical, varicose, or cystic).[25] The MAGELLAN trial was conducted from 2007 to 2010 and at that time there were no validated scores available (eg, bronchiectasis severity index, FACED score) that could have identified the clinical cases of bronchiectasis with a higher risk of mortality.[26–28] A better understanding of the etiopathogenesis of bronchiectasis is needed to improve the ability to provide thromboprophylaxis recommendations with a better benefit-risk profile.

Pulmonary hemorrhage overall and fatal pulmonary hemorrhage are rare but have been observed with rivaroxaban in post marketing reports. However, post marketing reports generally provide a limited medical history due to the voluntary reporting process, and an estimation of the exact percentage of patients treated with rivaroxaban who have a history of bronchiectasis and who subsequently experience pulmonary hemorrhage is not possible. Overall, of all spontaneous serious bleeding reports in safety surveillance through May 2020, less than 1% reported pulmonary hemorrhage as the location of bleeding. Nevertheless, due to the increase in bleeding in patients in MAGELLAN with bronchiectasis, the Food and Drug Administration specifically excluded patients with bronchiectasis in the new indication for extended thromboprophylaxis with rivaroxaban in patients hospitalized for the treatment of medical illnesses.

As more knowledge is gained in the bronchiectasis field and exposure to direct oral anticoagulants (DOACs) continues to accumulate, additional analyses using real-world data may be explored to conduct a complete analysis of bleeding with rivaroxaban in patients with bronchiectasis.

Conclusion

The results of this post hoc analysis of the MAGELLAN trial suggest that rivaroxaban does not have a favorable benefit-risk profile for primary thromboprophylaxis in acutely ill medical patients with bronchiectasis compared with standard dose enoxaparin. Further studies are required to evaluate the severity and type of bronchiectasis that could place patients at a high risk of harm with rivaroxaban. Until additional data are available, an alternative thromboprophylaxis approach should be considered in these patients. Hospitalized patients with bronchiectasis requiring extended thromboprophylaxis would not likely have a positive benefit-risk profile from treatment with a DOAC and alternative anticoagulants or type of thromboprophylaxis should be utilized.

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