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

Concetta Lipardi, MD, PhD1, C. Gregory Elliott, MD2, Chiara L. Sugarmann, BSN, MSHS1, Lloyd Haskell, MD1, Alex C. Spyropoulos, MD3,4,5,6, Gary E. Raskob, PhD6, Jianfeng Xu, PhD1, Wentao Lu, PhD1, Jessica Marsigiano, BS1, Theodore Spiro, MD7, Zhong Yuan, MD, PhD8, Shujian Wu, MD, PhD9, and Elliot S. Barnathan, MD1

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

1Janssen Research and Development, LLC, Raritan, NJ, USA
2Intermountain Medical Center, Murray, UT, USA
3The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA
4Anticoagulation and Clinical Thrombosis Services, Northwell Health at Lenox Hill Hospital, New York, NY, USA
5I.M. Sechenov First Moscow State Medical University, Moscow, Russia
6Hudson College of Public Health, University of Oklahoma Health Sciences Center, OK, USA
7Bayer US, LLC, Whippany, NJ, USA
8Janssen Research and Development, LLC, Titusville, NJ, USA
9Janssen Research and Development, LLC, Horsham, PA, USA

Corresponding Author:
Concetta Lipardi, Janssen Research & Development, LLC, 920 Route 202, Raritan, NJ 08869, USA.
Email: clipardi@its.jnj.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Introduction

Bronchiectasis is a chronic disease characterized by recurrent infection and inflammation of the bronchial tree. In the United States, there are currently over 110,000 people diagnosed with bronchiectasis and the prevalence of bronchiectasis increases with increasing age. 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.

The natural history of bronchiectasis includes chronic symptoms that worsen over time. 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. 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. In contrast, rivaroxaban, a Factor Xa inhibitor, has the advantage of being orally administered without dose adjustment or routine coagulation monitoring. 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. 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. 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/m². 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 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 ≥35 kg/m² (5.0% vs 15.4%), chronic venous insufficiency (9.9% vs 14.9%), severe varicosity (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                     | .493    |
|                                       | 69.0 ± 12.5 (56.0)            | 69.2 ± 12.0 (55.6)               |         |
| Male, sex (%)                         | 34 (56.7)                    | 30 (49.2)                       | .7902   |
|                                       | 64 (52.9)                    | 2189 (53.6)                     |         |
|                                       | 2073 (52.6)                  | 4262 (54.1)                     |         |
| Creatinine clearance                  |                              |                                 |         |
| 30 ≤ 50 mL/min                        | 16 (27.1)                    | 14 (24.6)                       | .1461   |
| 50-80 mL/min                          | 16 (27.1)                    | 21 (36.8)                       | .1461   |
| >80 mL/min                            | 26 (44.1)                    | 21 (36.8)                       | .1461   |
| Relevant medical history              |                              |                                 |         |
| COPD                                  | 36 (60)                      | 30 (49.2)                       | <.0001  |
| Asthma                                | 16 (26.7)                    | 14 (23.0)                       | .0058   |
| Acute respiratory failure             | 8 (13.3)                     | 9 (14.8)                        | .0001   |
| Respiratory failure                   | 10 (16.7)                    | 8 (13.1)                        | .0001   |
| Relevant medical history              |                              |                                 |         |
| Reason for hospitalization            |                              |                                 |         |
| Infectious disease                    | 51 (85.0)                    | 49 (80.3)                       | <.0001  |
| Heart failure                         | 13 (21.7)                    | 9 (14.8)                        | .0007   |
| Respiratory insufficiency             | 44 (73.3)                    | 46 (75.4)                       | <.0001  |
| Ischemic stroke                       | 0                            | 1 (1.6)                         | .0001   |
| Active cancer                         | 0                            | 1 (1.6)                         | .0001   |
| Inflammatory rheumatic disease        | 11 (1.7)                     | 1 (1.6)                         | .0001   |
| More than 1 diagnosis                 | 41 (68.3)                    | 42 (68.9)                       |         |
| VTE risk factors                      |                              |                                 |         |
| Acute infectious disease              | 28 (46.7)                    | 26 (42.6)                       | <.0001  |
| contributing to hospitalization       | 26 (42.6)                    | 54 (44.6)                       |         |
| Age ≥75 years                         | 24 (40.0)                    | 26 (42.6)                       | .5180   |
| History of heart failure              | 21 (35.0)                    | 18 (29.5)                       | .5935   |
| History of cancer                     | 5 (8.3)                      | 10 (16.4)                       | .1782   |
| Chronic venous insufficiency          | 7 (11.7)                     | 5 (8.2)                         | .1281   |
| Severe varicosis                      | 6 (10.0)                     | 3 (4.9)                         | .1255   |
| History of DVT or PE                  | 4 (6.7)                      | 2 (3.3)                         | .8821   |
| BMI ≥35 kg/m²                         | 3 (5.0)                      | 3 (4.9)                         | .0016   |
| Bleeding risk factors                 |                              |                                 |         |
| Active cancer reason for hospitalization | 0                  | 1 (1.6)                        | .0058   |
| Bleeding within 3 months              | 3 (5.0)                      | 5 (8.2)                         | .0347   |
| Active gastroduodenal ulcer within 3 months | 1 (1.7) | 2 (3.3) | .7808 |
| Use of dual antiplatelet at baseline  | 1 (1.7)                      | 1 (1.6)                         | .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. 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. 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. Although there are many comorbidities associated with bronchiectasis, COPD is the most frequent, as there is a large degree of overlap in these diseases. 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). 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. 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.

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. 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. 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...
| Category                      | Patients with bronchiectasis | Patients without bronchiectasis |
|-------------------------------|------------------------------|---------------------------------|
| Total VTE                     | N = 43, n (%)                | N = 48, n (%)                   |
| Rivaroxaban                   | 2924, n (%)                  | 2924, n (%)                     |
| Enoxaparin/Placebo            | 3009, n (%)                  | 3009, n (%)                     |
| Relative risk (95% CI)        | 126 (4.3)                    | 173 (5.8)                       |
| Rivaroxaban                   | 2.36 (0.48-11.55)            | 132 (4.4)                       |
| Enoxaparin/placebo            | 99 (3.4)                     | 15 (0.5)                        |
| Asymptomatic DVT             | 2.36 (0.48-11.55)            | 132 (4.4)                       |
| Symptomatic DVT              | 2 (4.2)                      | 3.71 (0.40-34.05)               |
| Symptomatic PE               | 3.71 (0.40-34.05)            | 10 (0.3)                        |
| VTE-related Death            | 1 (2.3)                      | 18 (0.6)                        |
| 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 | Relative risk (95% CI) | Patients without bronchiectasis | Relative risk (95% CI) |
|-----------------------------------------------|------------------------------|-------------------------|---------------------------------|-------------------------|
|                                               | Rivaroxaban N = 60, n (%)    | Enoxaparin/placebo N = 61, n (%) | Rivaroxaban N = 3937, n (%)     | Enoxaparin/placebo N = 3940, n (%) |
| Treatment emergent major bleeding             | 3 (5.0)                      | 0                       | 40 (1.0)                       | 15 (0.4)                | 2.67 (1.48-4.82) |
| A fall in hemoglobin ≥2 g/dL                  | 1 (1.7)                      | 0                       | 30 (0.8)                       | 10 (0.3)                | 3.00 (1.47-6.12) |
| A transfusion ≥2 units of blood               | 1 (1.7)                      | 0                       | 23 (0.6)                       | 8 (0.2)                 | 2.87 (1.29-6.41) |
| At a critical site                            | 0                            | 0                       | 9 (0.2)                        | 4 (0.1)                 | 2.25 (0.70-7.32) |
| Fatal                                         | 3 (5.0)                      | 0                       | 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.
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). 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. 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.

**Acknowledgments**

The authors would like to thank the patients who participated in the MAGELLAN trial for their contribution to the content of this.
manuscript. Concetta Lipardi, MD, PhD, is the corresponding author. All authors have 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, Discussion; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that the questions related to the accuracy and integrity of any part.

Authors' Note
Role of the sponsors: Bayer U.S. LLC and Janssen Research and Development LLC sponsored the MAGELLAN study and the analysis reported here. The institutional review board or ethics committee at each participating center approved the protocol, and all the patients provided written informed consent. C. Lipardi: Employment and Equity Ownership; Janssen R&D LLC. C.G. Elliott: Consultant/ Honoraria; Janssen R&D LLC; Employment Intermountain Healthcare. C. Sugarmann: Employment and Equity Ownership; Janssen R&D LLC. L. Haskell: Employment and Equity Ownership; Janssen R&D LLC. A.C. Spyropoulos: Consultancy/Research Funding; Boehringer Ingelheim, Janssen R&D, LLC; Consultancy; Daiichi Sankyo, Portola, Bayer, ATLAS (Colorado Prevention Center). G.E. Raskob: Consultant/Honoraria; Janssen R&D LLC, Bayer, BMS, Daiichi Sankyo, Pfizer; Consultancy; Boehringer Ingelheim, Eli Lilly, Portola, Novartis, Anthos, Tetherex. J. Xu: Former employment and Equity Ownership; Janssen R&D LLC. W. Lu: Employment and Equity Ownership; Janssen R&D LLC. J. Marsigiano: Employment and Equity Ownership; Janssen R&D LLC. T.E. Spiro: Former employment Bayer Healthcare US LLC. Z. Yuan: Employment and Equity Ownership; Janssen R&D LLC. S. Wu: Employment and Equity Ownership; Janssen R&D LLC. E.S. Barnathan: Employment and Equity Ownership; Janssen R&D LLC.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Bayer U.S. LLC and Janssen Research and Development LLC who sponsored the MAGELLAN study and the analysis reported here.

ClinicalTrials.gov Number
NCT 00571649.

ORCID iDs
Concetta Lipardi https://orcid.org/0000-0002-3815-2259
Chiara L. Sugarmann https://orcid.org/0000-0003-2040-6983
Alex C. Spyropoulos https://orcid.org/0000-0002-3175-461X
Jessica Marsigiano https://orcid.org/0000-0003-3750-4424

References
1. O’Donnell AE. Bronchiectasis. Chest. 2008;134:815-823.
2. Chalmers JD. New insight into the epidemiology of bronchiectasis. Chest. 2018;154:1272-1273.
3. Addrizzo-Harris D, Barrios C, Gadotra S, et al. Bronchiectasis. Chest Foundation website. 2020. Accessed June 11, 2020.
4. Quint JK, Millett ER, Joshi M, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. Eur Respir J. 2016;47:186-193.
5. Henkle E, Chan B, Curtis JR, Aksamit TR, Daley CL, Winthrop KL. Characteristics and health-care utilization history of patients with bronchiectasis in US Medicare enrollees with prescription drug plans, 2006 to 2014. Chest. 2018;154:1311-1320.
6. Aksamit TR, O’Donnell AE, Barker A, et al. Adult patients with bronchiectasis: a first look at the US Bronchiectasis Research Registry. Chest. 2017;151:982-992.
7. Polverino E, Goeminnie PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017;50:1700629.
8. Tino G. Bronchiectasis: phenotyping an orphan disease. Am J Respir Crit Care Med. 2018;197:1371-1373.
9. Dweik RA, Stoller JK. Role of bronchoscopy in massive hemoptysis. Clin Chest Med. 1999;20:89-105.
10. McGarry LJ, Stokes ME, Thompson D. Outcomes of thromboprophylaxis with enoxaparin vs. unfractionated heparin in medical inpatients. Thrombosis J. 2006;4:17.
11. Perzborn E, Roehrig S, Straub A, et al. Rivaroxaban: a new oral factor Xa inhibitor. Arterioscler Thromb Vasc Biol. 2010;30:376-381.
12. Cohen AT, Spiro TE, Büller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med. 2013;368:513-523.
13. Cohen AT, Spiro TE, Büller HR, et al. Extended-duration rivaroxaban thromboprophylaxis in acutely ill medical patients: MAGELLAN study protocol. J Thromb Thrombolysis. 2011;31:407-416.
14. Spyropoulos AC, Lipardi C, Xu J, et al. Improved benefit risk profile of rivaroxaban in a subgroup population of the MAGELLAN study. Clin Appl Thromb Hemost. 2019;25(4):107602961988602.
15. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719-748.
16. Pauporté MC, Helliwell SM, Houghton SJ, et al. An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med. 2000;162:1277-1284.
17. Chalmers JD, Aliberti S, Filoneko A, et al. Characterization of the “frequent exacerbator phenotype” in bronchiectasis. Am J Respir Crit Care Med. 2018;29(11):1410-1420.
18. Chalmers JD. Happy Birthday, Bronchiectasis: 200 years of targeting mucus. Am J Respir Crit Care Med. 2020;201:639-640.
19. Steinberg M, Flume PA, Chalmers JD. Is bronchiectasis really a disease? Eur Respir Rev. 2020;29:190051.
20. Martinez-Garcia MA, Polverino E, Aksamit T. Bronchiectasis and chronic airflow disease. Chest. 2018;154:737-739.
21. Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of COVID-19: a systematic review and meta-analysis. J Med Virol. 2020;1-7.
22. Fraser E. Long term respiratory complications of Covid-19. BMJ. 2020;370:m3001.
23. Qi Q, Li T, Li JC, Li Y. Association of body mass index with disease severity and prognosis in patients with non-cystic fibrosis bronchiectasis. *Braz J Med Biol Res.* 2015;48:715-724.

24. Wang X, Liu B, Wang D, Liu C. Risk factors for haemoptysis in 1804 adults with non-cystic fibrosis bronchiectasis in Southwestern China: a retrospective cohort study. *Am J Respir Crit Care Med.* 2019;199:A5711.

25. Milliron B, Henry TS, Veeraraghavan S, Little B. Bronchiectasis: mechanisms and imaging clues of associated common and uncommon diseases. *Radiographics.* 2015;35:1011-1030.

26. Chalmers JD, Goeminne P, Aliberti S, et al. The Bronchiectasis Severity Index: an international derivation and validation study. *Am J Respir Crit Care Med.* 2014;189:576-585.

27. Martinez-Garcia MA, de Gracia J, Vendrell Relat M, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. *Eur Respir J.* 2014;43:1357-1367.

28. Hill AT, Haworth CS, Aliberti S, et al. EMBARC/BRR Definitions Working Group. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J.* 2017;49:170051.