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ORIGINAL ARTICLE

D-dimer as a predictor of venous thromboembolism in acutely ill, hospitalized patients: a subanalysis of the randomized controlled MAGELLAN trial

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Summary. *Background:* D-dimer concentrations have not been evaluated extensively as a predictor of increased venous thromboembolism (VTE) risk in acutely ill, hospitalized medical patients. *Objectives:* To analyze the relationships between D-dimer concentration, VTE and bleeding in the MAGELLAN trial (NCT00571649). *Patients/methods:* This was a multicenter, randomized, controlled trial. Patients aged ≥ 40 years, hospitalized for acute medical illnesses with risk factors for VTE received subcutaneous enoxaparin 40 mg once daily for 10 ± 4 days then placebo up to day 35, or oral rivaroxaban 10 mg once daily for 35 ± 4 days. Patients (n = 7581) were grouped by baseline D−dimer ≤ 2 × or > 2 × the upper limit of normal. VTE and major plus non-major clinically relevant bleeding were recorded at day 10, day 35, and between days 11 and 35. *Results:* The frequency of VTE was 3.5-fold greater in patients with high D-dimer concentrations. Multivariate analysis showed that D-dimer was an independent predictor of the risk of VTE (odds ratio 2.29 [95% confidence interval 1.75–2.98]), and had a similar association to established risk factors for VTE, for example cancer and advanced age. In the high D-dimer group, rivaroxaban was non-inferior to enoxaparin at day 10 and, unlike the low D-dimer group, superior to placebo at day 35 ($P < 0.001$) and days 11–35 ($P < 0.001$). In both groups, bleeding outcomes favored enoxaparin/placebo. *Conclusions:* Elevated baseline D-dimer concentrations may identify acutely ill, hospitalized medical patients at high risk of VTE for whom extended anticoagulant prophylaxis may provide greater benefit than for those with low D-dimer concentrations.

Keywords: D-dimer; enoxaparin; hospitalization; rivaroxaban; venous thromboembolism.

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Introduction

Acutely ill, hospitalized medical patients, such as those with active cancer or those who have experienced a stroke, acute heart failure, infection, inflammation or respiratory failure, are at substantial risk of venous thromboembolism (VTE) [1]. Studies have shown that this risk may continue beyond the standard duration of anticoagulant therapy [2–4], but determining the optimal duration of thromboprophylaxis in this heterogeneous patient population is challenging [3–5].

Three randomized clinical trials have investigated the use of extended anticoagulant therapy in acutely ill, hospitalized medical patients. In the EXCLAIM study, after an initial open-label 10 ± 4 day course of enoxaparin, a further 28 ± 4 days of therapy significantly reduced the overall incidence of VTE compared with placebo [4]. Subsequently, the MAGELLAN study investigated the effect

on VTE incidence of extended prophylaxis (35 ± 4 days) using the oral, direct factor Xa inhibitor rivaroxaban compared with standard-duration subcutaneous enoxaparin (10 ± 4 days) followed by oral placebo [6]. In MAGELLAN, rivaroxaban was shown to be non-inferior compared with enoxaparin at day 10 in terms of VTE incidence, and superior to enoxaparin followed by placebo at day 35 [3]. The ADOPT study investigated the effect on VTE risk of thromboprophylaxis with apixaban given for 30 days compared with enoxaparin given for between 6 and 14 days, but failed to show superiority for the extended apixaban regimen [5].

In all three studies, overall bleeding rates were low. However, the extended prophylaxis regimens carried a significantly increased risk of major bleeding in EXCLAIM and ADOPT and of clinically relevant bleeding (major plus non-major clinically relevant bleeding) in MAGELLAN vs. the comparator arms. Therefore, for all three studies, the benefit–risk balance for extended thromboprophylaxis in the overall study populations was not favorable [3–5].

A preliminary univariate analysis of the MAGELLAN data identified baseline D-dimer concentration as an independent predictive factor for VTE (data on file). D−dimer is a fibrin degradation product that occurs as a result of thrombus fibrinolysis [7], and elevated concentrations have previously been associated with an increased risk of VTE in acutely ill patients [8,9]. Because D-dimer is a sensitive (typically 85–95%, dependent on assay) but non-specific (50–70%) marker of thrombosis that is widely used in clinical practice as a diagnostic aid for suspected VTE [7,10], it was hypothesized that D-dimer concentrations could be employed to identify a subgroup of acutely ill patients at high risk of VTE for whom the benefit–risk balance of extended thromboprophylaxis might be favorable. In this subanalysis, the relationship between D-dimer concentrations, thromboprophylaxis and efficacy and safety outcomes in the MAGELLAN study were evaluated.

Methods

Study design and endpoints

The MAGELLAN protocol and inclusion criteria have been reported previously [6]. Briefly, patients aged ≥ 40 years who were hospitalized for various acute medical illnesses with risk factors for VTE, and who had an anticipated survival of > 6 months, were randomized to receive either subcutaneous enoxaparin 40 mg once daily for 10 ± 4 days followed by placebo up to day 35, or oral rivaroxaban 10 mg once daily for 35 ± 4 days.

The primary efficacy endpoints were the composite incidence of asymptomatic proximal deep vein thrombosis, symptomatic deep vein thrombosis, symptomatic nonfatal pulmonary embolism and VTE-related death up to day 10 and day 35. The principal safety outcome was the composite of treatment-emergent major bleeding and non-major clinically relevant bleeding at day 10 and day 35. Overt bleeding episodes falling outside these criteria, on-treatment adverse events and laboratory parameters were secondary safety outcomes [6].

As per protocol, D-dimer concentrations were determined at baseline (day 1; prior to receiving the first dose of study medication and between 2 and 4 h afterwards) and on day 10 pre- and post-dose. The pre-dose concentration was used unless missing, in which case the post-dose value was used. All analyses were conducted at a central laboratory using the STA Liatest D-DI (Diagnostica Stago, Asnières-sur-Seine, France) assay, which has an upper limit of normal (ULN) of 0.5 μg mL^{-1}. This is a quantitative assay of D-dimer antigen in citrated plasma by the immunoturbidimetric method based on measurement of light absorbance produced by a suspension of microlatex particles coated with specific mouse anti-human D-dimer monoclonal antibodies. The results of D-dimer tests were not provided to treating physicians.

Subanalysis design and endpoints

In MAGELLAN, the overall median baseline D-dimer concentration was 0.94 μg mL^{-1}, which corresponds to approximately twice the ULN. Therefore, patients were grouped *post-hoc* according to whether their D-dimer concentration was ≤ 2 × ULN or > 2 × ULN, and a multivariate analysis was conducted using this cut-off. The multivariable logistic regression model included treatment group and D-dimer concentration at baseline, and applied a stepwise variable selection (using an entry level of $P = 0.3$, which was considered appropriate based on exploratory analyses) for additional covariates including sex, age ≥ 75 years, body mass index, creatinine clearance, geographic region, all acute medical conditions present, baseline high-sensitivity C−reactive protein, history of VTE, and recent major surgery. Receiver operating characteristic (ROC) analysis was performed for the incidence of VTE at day 10 and day 35; the area under the ROC curve for D-dimer at baseline and the positive and negative predictive values, sensitivity and 1-specificity were derived; ROC results were also derived for two other VTE risk scores for hospitalized medical patients – IMPROVE [11] and PRETEMED [12,13] – to evaluate the predictive value of baseline D-dimer for VTE.

Venous thromboembolism and major and non-major clinically relevant bleeding were analyzed for the group of patients with a baseline D-dimer concentration > 2 × ULN (the high D-dimer group) and for those with a baseline D-dimer concentration ≤ 2 × ULN (the low D−dimer group). An exploratory analysis of the above outcomes by D-dimer concentration occurring during the extended prophylaxis period (days 11–35) was also conducted. Criteria for inclusion in the populations evalu-

ated for efficacy and safety have been reported previously [6]. The per-protocol population was the primary population used for analysis of non-inferiority at day 10, whereas the modified intention-to-treat population was the efficacy population for superiority analysis at day 35. The safety population comprised all patients who received a study drug. In the current analysis, the efficacy population was used for *post-hoc* evaluation of efficacy during the extended prophylaxis period.

Statistical methods

In the analyses presented here, for VTE and bleeding outcomes, relative risk (RR) ratios (rivaroxaban vs. enoxaparin or rivaroxaban vs. enoxaparin/placebo) were estimated based on asymptotic methods. If not noted otherwise, two-sided P values and two-sided 95% confidence intervals (CIs) were calculated for tests.

Study oversight, registration and role of the funding source

The MAGELLAN study was conducted in accordance with the Declaration of Helsinki and local regulations. The protocol was approved by the local Institutional Review Board or Ethics Committee and written informed consent was obtained from each patient prior to any study-specific procedures. The study was supported by research funding from Bayer HealthCare Pharmaceuticals and Janssen Research & Development, LLC to the MAGELLAN study group, and was designed and supervised by the MAGELLAN Steering Committee. Data were collected and analyzed by the study sponsors. All authors contributed to writing the manuscript, had full access to the data and analyses, and vouch for the accuracy and completeness of the report. The Steering Committee made the decision to publish. This trial was registered at www.clinicaltrials.gov as NCT00571649.

Results

Baseline patient characteristics by D-dimer concentration

MAGELLAN randomized 8101 patients from 556 sites in 52 countries between December 2007 and July 2010 (Fig. S1) [3]. Of these, 7581 patients had D-dimer measurements (of which the post-dose D-dimer value was used in 7.6% and 5.3% of patients valid for safety analysis at baseline and day 10, respectively). Baseline characteristics by D-dimer concentration are shown in Table 1. Compared with the low D-dimer group, patients in the high D-dimer group were slightly older, had a lower body mass index, and had a higher incidence of heart failure, active cancer, infection or inflammation, and additional risk factors for VTE, but a lower incidence of acute ischemic stroke and respiratory insufficiency.

Venous thromboembolism by D-dimer concentration

D-dimer concentrations at baseline and day 10 for patients with or without VTE at day 10 and day 35 are shown in Table 2; patients with VTE had a mean baseline D-dimer concentration that was higher than those who did not. Patients with high D-dimer concentrations at baseline and day 10 were more likely to have VTE by day 35 than those with lower concentrations, regardless of treatment (Fig. S2). Overall, 106 of 2662 (4.0%) patients in the high D-dimer group had a venous thromboembolic event by day 10, compared with 35 of 3037 (1.2%) in the low D-dimer group. The absolute VTE rate increased with rising baseline D-dimer concentration in both study arms, and was more pronounced with enoxaparin than rivaroxaban at day 10 (data not shown) and with enoxaparin/placebo at day 35 (Fig. 1).

The outcome of the multivariate analysis at day 35 confirmed that D-dimer concentration $> 2 \times$ ULN compared with $\leq 2 \times$ ULN was an independent predictor of

Table 1 Patient characteristics at entry by baseline D-dimer concentration (safety population)

Baseline D-dimer concentration	$> 2 \times$ ULN (high D-dimer group)		$\leq 2 \times$ ULN (low D-dimer group)	
Parameter	Rivaroxaban $n = 1781$	Enoxaparin/placebo $n = 1834$	Rivaroxaban $n = 2003$	Enoxaparin/placebo $n = 1963$
Age, mean, years	71.4	71.3	67.3	67.2
Weight, mean, kg	75.2	75.8	79.1	78.8
Height, mean, cm	165.0	165.0	166.0	165.0
BMI, mean, kg m^{-2}	27.5	27.7	28.7	28.7
Male,%	53.1	49.6	58.4	55.7
Heart failure, %	34.5	36.4	30.7	29.8
Active cancer, %	9.0	8.5	6.0	6.0
Acute ischemic stroke, %	11.5	11.5	22.8	22.9
Infection/inflammation, %	52.4	51.5	42.8	42.0
Respiratory insufficiency, %	25.7	27.5	27.7	29.9
Additional risk factor for VTE, %	45.3	44.1	40.6	41.5

BMI, body mass index; ULN, upper limit of normal; VTE, venous thromboembolism.

Table 2 D-dimer concentrations at baseline and day 10 for patients with and without VTE at days 10 and 35

Time point/outcome	Rivaroxaban			Enoxaparin/placebo		
	n	D-dimer concentration, μg mL^{-1} mean (SD)	95% CI	*n*	D-dimer concentration, μg mL^{-1} mean (SD)	95% CI
Baseline D-dimer						
Day 10 with VTE*	77	2.14 (1.34)	1.84–2.45	77	2.48 (1.39)	2.16–2.79
Day 10 without VTE*	3707	1.35 (1.13)	1.31–1.39	3720	1.35 (1.13)	1.32–1.39
Day 35 with VTE†	122	2.07 (1.30)	1.83–2.30	161	2.24 (1.28)	2.04–2.44
Day 35 without VTE†	3662	1.34 (1.13)	1.31–1.38	3636	1.34 (1.13)	1.30–1.37
Days 11–35 with VTE†	66	1.84 (1.24)	1.53–2.14	106	2.24 (1.25)	1.99–2.48
Days 11–35 without VTE†	3718	1.36 (1.14)	1.32–1.40	3691	1.35 (1.14)	1.31–1.39
Day 10 D-dimer						
Day 35 with VTE†	92	1.67 (1.25)	1.41–1.93	138	1.70 (1.15)	1.51–1.89
Day 35 without VTE†	3221	1.03 (1.01)	1.00–1.07	3233	1.01 (0.96)	0.98–1.05
Days 11–35 with VTE†	52	1.69 (1.30)	1.33–2.06	98	1.71 (1.10)	1.49–1.93
Days 11–35 without VTE†	3261	1.04 (1.01)	1.00–1.07	3273	1.02 (0.97)	0.99–1.05

CI, confidence interval; SD, standard deviation; VTE, venous thromboembolism. *Per-protocol population. †Efficacy population.

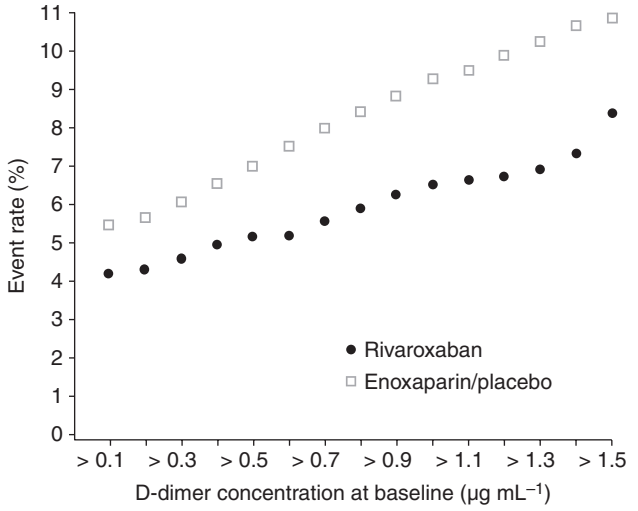

Fig. 1. Absolute event rate for venous thromboembolism at day 35 by treatment arm and baseline D-dimer concentration. Results are shown for the efficacy population.

the risk of VTE (odds ratio [OR], 2.29; 95% CI, 1.75–2.98; Table 3). The area under the ROC curve for D-dimer at baseline ranged between 0.67 and 0.74, depending on the day of VTE assessment and treatment group, with larger values for enoxaparin and placebo than for rivaroxaban (Table S1 and Fig. S3). Baseline D-dimer concentration had a similar predictive value for VTE to the IMPROVE risk score at admission and during hospitalization, and the PRETEMED risk score, when applied to the MAGELLAN data (Table S2).

Venous thromboembolism incidence by D-dimer group is shown in Figs 2 and 3. In the primary analysis, rivaroxaban was non-inferior to enoxaparin (prespecified RR margin of 1.5) at day 10 in the overall study population for VTE incidence (2.7% in both arms; RR = 0.97; 95% CI, 0.71–1.31), and superior to enoxaparin/placebo at day 35 (4.4% vs. 5.7%, respectively; RR = 0.77; 95% CI, 0.62–0.96; $P = 0.02$) [14]. In this analysis, rivaroxaban remained non-inferior to enoxaparin at day 10 in both D-dimer groups: high D-dimer group, 49/1312 (3.7%) and 57/1350 (4.2%) patients with VTE for rivaroxaban and enoxaparin, respectively; low D-dimer group, 20/1517 (1.3%) and 15/1520 (1.0%) patients, respectively. At day 35, rivaroxaban was superior to enoxaparin/placebo in the high D-dimer group (VTE incidence rates of 84/1285 [6.5%] vs. 125/1348 [9.3%], respectively), whereas rates in the low D-dimer group were similar between the treatment arms (36/1558 [2.3%] vs. 35/1573 [2.2%], respectively).

In the extended prophylaxis period (days 11–35), rivaroxaban was superior to placebo in the high D-dimer group (43/1259 [3.4%] vs. 84/1321 [6.4%], respectively). In contrast, and as seen with the above analyses, patients in the low D-dimer group had similar incidences of VTE in both study arms (22/1553 [1.4%] vs. 21/1563 [1.3%], respectively).

Safety outcomes by D-dimer concentration

Bleeding outcomes by D-dimer group are shown in Fig. 2. In the overall MAGELLAN study population, major or non-major clinically relevant bleeding occurred in 2.8% of patients given rivaroxaban and 1.2% of patients given enoxaparin at day 10 (RR = 2.3; 95% CI, 1.63–3.17; $P < 0.001$) [14]. In the high D-dimer group, major or non-major clinically relevant bleeding occurred with an incidence of 3.4% (61/1781) in the rivaroxaban arm and 1.7% (31/1834) in the enoxaparin arm at day 10 (RR = 2.03; 95% CI, 1.32–3.11; $P = 0.001$), and 2.0% (41/2003) and 0.9% (17/1963), respectively, in the low D-dimer group (RR = 2.36; 95% CI, 1.35–4.15; $P = 0.003$).

At day 35, rates of major or non-major clinically relevant bleeding in the overall population were 4.1% among

Table 3 Multivariate logistic regression analysis of VTE up to day 35 (efficacy population)

Covariate	Likelihood ratio test			Comparison for odds ratio	Odds ratio	95% CI
	Degree(s) of freedom	Chi square	*P* value			
History of DVT/PE	1	67.42	< 0.001	Yes vs. no	5.00	3.55–7.05
Recent major surgery*	1	5.29	0.022	Yes vs. no	3.08	1.30–7.25
Baseline D-dimer concentration	1	39.16	< 0.001	> 2 × ULN vs. ≤ 2 × ULN	2.29	1.75–2.98
Active cancer	1	9.34	0.002	Yes vs. no	1.97	1.31–2.97
Creatinine clearance group at enrolment, mL min^{-1}	3	13.54	0.004	< 30 vs. > 80	0.52	0.15–1.75
				30–< 50 vs. > 80	1.76	1.22–2.54
				50–≤ 80 vs. > 80	1.19	0.87–1.64
Age ≥ 75 years	1	8.54	0.004	Yes vs. no	1.53	1.15–2.04
Baseline hs–CRP	1	9.86	0.002	> Median vs. ≤ median†	1.49	1.16–1.91
Sex	1	0.04	0.83	Female vs. male	1.03	0.80–1.31
Treatment group	1	4.98	0.026	Rivaroxaban vs. enoxaparin/placebo	0.76	0.60–0.97
Acute respiratory insufficiency	1	4.71	0.03	Yes vs. no	0.72	0.54–0.98

CI, confidence interval; DVT, deep vein thrombosis; hs–CRP, high-sensitivity C-reactive protein; PE, pulmonary embolism; ULN, upper limit of normal; VTE, venous thromboembolism. *Within 6–12 weeks. †Includes missing values.

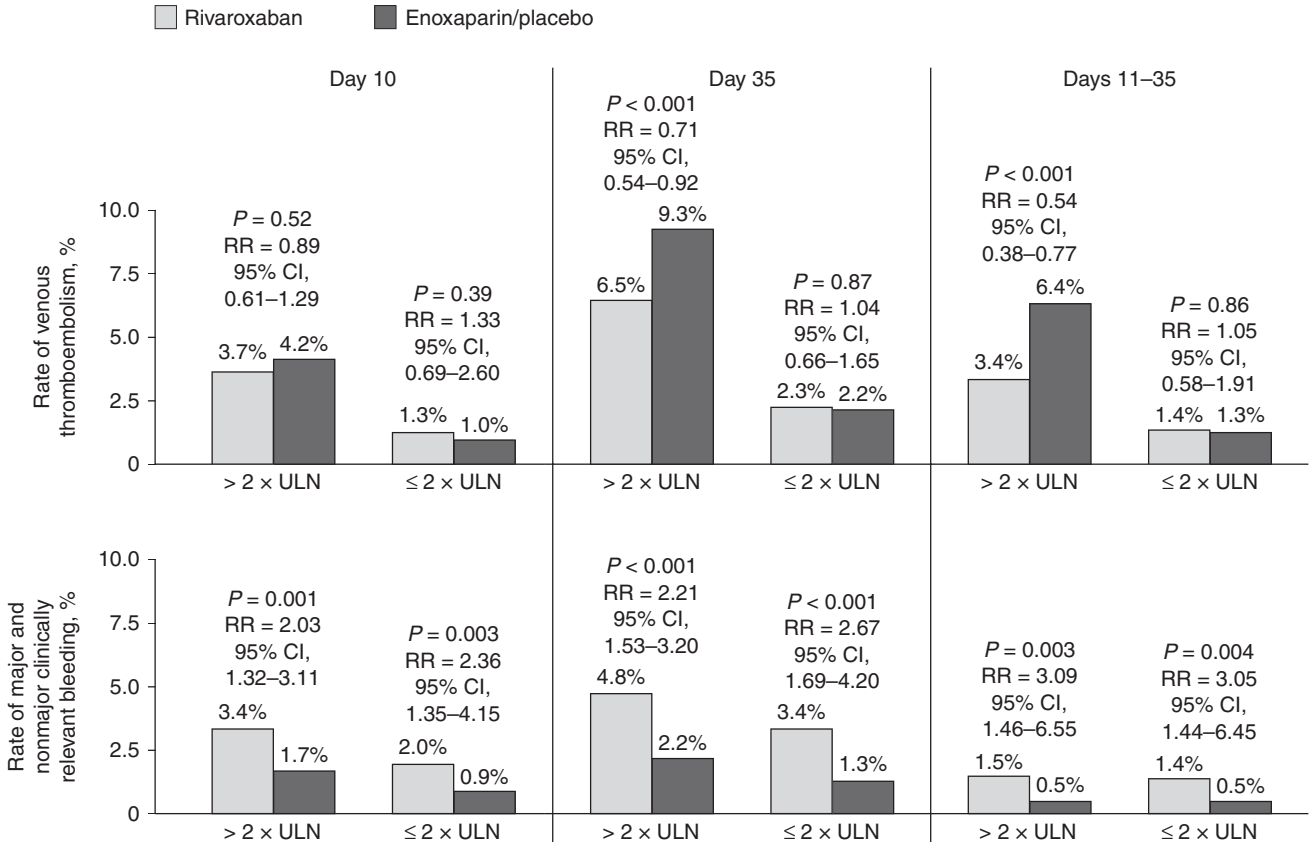

Fig. 2. Rates and relative risks of VTE and major plus non-major clinically relevant bleeding at day 10, day 35 and days 11–35. Effect shown by baseline D-dimer concentration > 2 × ULN vs. ≤ 2 × ULN. CI, confidence interval; RR, relative risk; ULN, upper limit of normal; VTE, venous thromboembolism.

rivaroxaban recipients and 1.7% among enoxaparin/placebo recipients [14]. For patients in the high D-dimer group, the equivalent rates at day 35 were 4.8% (86/1781) and 2.2% (40/1834; RR = 2.21; 95% CI, 1.53–3.20; $P < 0.001$). These rates were 3.4% (68/2203) and 1.3% (25/1963), respectively, for the low D-dimer group (RR = 2.67; 95% CI, 1.69–4.20; $P < 0.001$). In the day 11–35 analysis, major plus non-major clinically relevant bleeding occurred at similar rates for rivaroxaban and placebo in the high and low D-dimer groups: 1.5% (27/1781) vs.

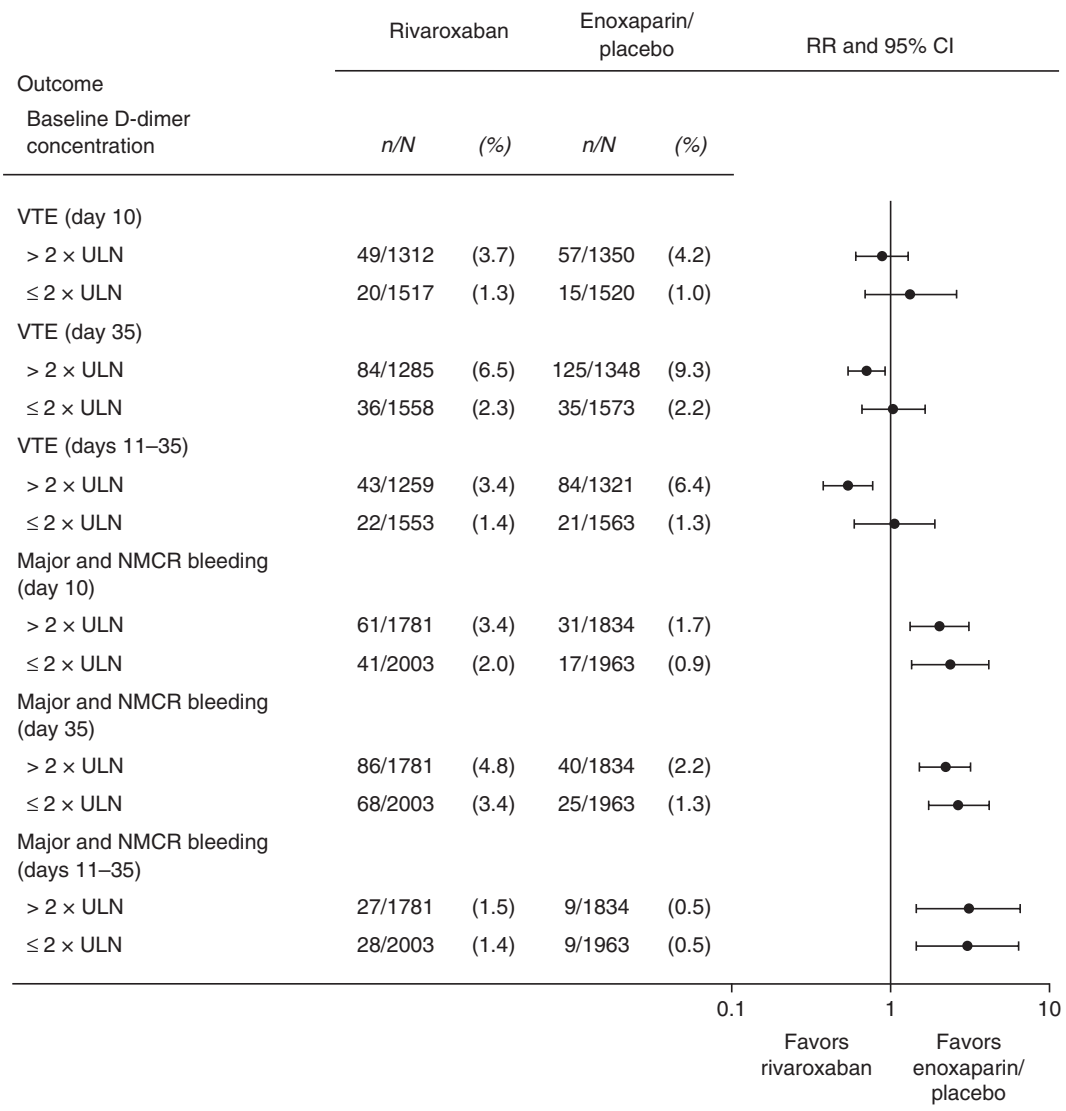

Fig. 3. Outcomes and relative risks by time-point for the high and low D-dimer groups. Venous thromboembolism and major plus non-major clinically relevant bleeding. CI, confidence interval; NMCR, non-major clinically relevant; RR, relative risk; ULN, upper limit of normal.

0.5% (9/1834) in the high D-dimer group (RR = 3.09; 95% CI, 1.46–6.55; $P = 0.003$) and 1.4% (28/2003) vs. 0.5% (9/1963) in the low D-dimer group (RR = 3.05; 95% CI, 1.44–6.45; $P = 0.004$).

Overall mortality at day 35 was greater in the high D-dimer group (5.7% [102/1781] for rivaroxaban vs. 5.7% [104/1834] for enoxaparin/placebo) than the low D-dimer group (2.2% [45/2003] vs. 2.0% [40/1963]), and the incidence of all adverse events was also slightly higher (high D-dimer, 1243/1781 [69.8%] for rivaroxaban vs. 1288/1834 [70.2%] for enoxaparin/placebo; low D-dimer, 1320/2003 [65.9%] vs. 1254/1963 [63.9%], respectively). Rates for liver function abnormalities up to day 35 varied minimally by D-dimer group and were similar between the rivaroxaban and enoxaparin/placebo treatment arms; among patients with high baseline D-dimer concentrations, aspartate aminotransferase was elevated by > 3 × ULN vs. baseline in 15/1511 (1.0%) patients in the rivaroxaban arm and 18/1537 (1.2%) patients in the enoxaparin/placebo arm; for patients with low baseline D-dimer concentrations, these rates were 11/1758 (0.6%) and 17/1758 (1.0%) patients, respectively. Similar results were found for alanine aminotransferase and bilirubin concentrations.

Discussion

The MAGELLAN study provides the largest D-dimer dataset (7581 patients with evaluable concentrations) accumulated in acutely ill, hospitalized medical patients, from which the relationship between D-dimer concentration and risk of VTE, and the effect of thromboprophylaxis on this risk, has been evaluated. This analysis shows that the risk of VTE increases with rising D-dimer

concentration, and patients with a baseline D-dimer concentration > 2 × ULN are at a 3.5-fold higher risk of VTE than those with concentrations ≤ 2 × ULN. Elevated D-dimer concentrations at day 10 were associated with an increased risk of VTE up to day 35. Multivariate analysis confirmed that baseline D-dimer concentration is an independent predictor of VTE risk (OR = 2.29 [95% CI, 1.75–2.98]) after adjustment for other known risk factors, and had a similar association to the established risk factors for VTE of cancer (OR = 1.97 [95% CI, 1.31–2.97]) and age ≥ 75 years (OR = 1.53 [95% CI, 1.15–2.04]).

The area under the ROC curve for D-dimer at baseline (0.67–0.74) indicated that D-dimer concentration had a similar predictive value for VTE to validated scores for assessing the risk of VTE in acutely ill, hospitalized medical patients, namely IMPROVE (0.59–0.65) [11] and PRETEMED (0.54–0.56) [12,13]. It may be possible to create a similar score incorporating D-dimer and other variables to predict the risk of VTE in hospitalized patients. In particular, high D-dimer levels have been shown to be predictive of VTE risk and mortality in patients with cancer [15,16]. However, it was not possible to postulate such a score using the MAGELLAN data because the study was insufficiently powered to allow for a validation cohort in the control arm.

These observations corroborate those of the MEDENOX D-dimer subanalysis in 224 acutely ill, hospitalized medical patients [8]. In patients who had VTE, median D-dimer concentrations were significantly higher both at baseline (day 0; $P = 0.01$) and at day 10 ($P < 0.001$) than in patients without VTE, and all events occurred in patients who had elevated D-dimer concentrations at day 0 and day 10 [8]. More recently, a Chinese study in 458 elderly patients also indicated a significant association between elevated D-dimer concentration and VTE [9]; multivariate analysis showed that patients with raised baseline D-dimer concentrations had a 3.2-fold increased risk (95% CI, 1.5–6.5; $P = 0.002$) of VTE compared with patients with a normal baseline D-dimer.

In the MAGELLAN primary efficacy analysis, rivaroxaban was non-inferior to enoxaparin at day 10 and superior to enoxaparin/placebo at day 35 for reductions in VTE, although the incidence of clinically relevant bleeding was higher [3]. In this analysis, non-inferiority was maintained for the high D-dimer group at day 10, and a more substantial reduction in VTE was achieved at day 35: rivaroxaban treatment led to reductions of 29% in RR and 2.8% in absolute risk over enoxaparin/placebo. This benefit was maintained during the extended prophylaxis period (days 11–35, rivaroxaban vs. placebo), with reductions in relative and absolute risk of 46% and 3%, respectively. As in the overall population, incidence rates for major or non-major clinically relevant bleeding remained higher for rivaroxaban than for enoxaparin and placebo in both D-dimer groups at all time-points analyzed. These results suggest that continuing anticoagulant prophylaxis beyond day 10 could be considered in patients with high baseline D-dimer concentrations but would be unlikely to benefit those whose baseline D-dimer concentrations were low. It could be argued that determination of D-dimer concentration at the end of the usual 10-day prophylaxis period might provide a better indication of whether continued therapy is warranted than pretreatment values. However, it is likely to be impractical to collect samples and conduct D-dimer assays at or after hospital discharge and for this reason our study primarily concentrated on baseline D-dimer concentrations, which are routinely measured on admission.

Our study has limitations. This was a *post-hoc* analysis with a retrospectively defined cut-off for D-dimer concentration, and as such our results warrant prospective confirmation. An objective analysis, such as ultrasound imaging, was not routinely performed to prove the absence of thrombosis at the time of baseline D-dimer testing; however, this is consistent with the usual standard of care and thus reflects real-life clinical practice. D-dimer assays have varying sensitivity and specificity, and because sensitivity and cut-off points vary with the proprietary test, there is no standard for comparing one test with another. For this reason, a multiple of the ULN was chosen for the D-dimer cut-off in this study. However, it should be noted that newer generation tests, such as the enzyme-linked immunosorbent assay (ELISA) and quantitative latex agglutination methods, are highly sensitive (> 90%) and are superior to whole-blood D-dimer assays, latex semi-quantitative assays and latex qualitative assays [17]. A number of studies have shown that the STA Liatest D-DI assay used in MAGELLAN performs similarly to the ELISA D-dimer assay [18–20]. Although the use of a centralized laboratory necessitated the freezing and transportation of plasma samples, we performed stability studies that confirmed samples can be stored in this way for up to 18 months without affecting the results of D-dimer assays (data on file), a finding that is supported by an earlier published study [21]. Baseline D-dimer concentrations were missing in approximately 6.5% of patients, necessitating imputation of the post-dose value, but it should be noted that the latter measurements were taken on the same day as the first dose and would not be expected to show a relevant difference to the baseline value. Given that D-dimer assays are widely available and are used extensively in clinical practice to assist VTE diagnosis, D-dimer concentration represents a useful marker to aid clinical decision-making.

In summary, an elevated concentration of D-dimer measured soon after admission is independently associated with the risk of VTE in acutely ill, hospitalized medical patients. Elevated D-dimer was an independent predictor of VTE, and at least as predictive of VTE as other more complicated clinical scores. Medical patients

with high D-dimer levels have been identified not only as being at particularly high risk of VTE, but also as a group for whom anticoagulant prophylaxis may provide an improved benefit–risk profile compared with patients with low baseline D-dimer. Assessment of D-dimer at the end of the standard 10-day prophylaxis period may also provide an indication of risk and benefit from extended thromboprophylaxis. However, the increased bleeding risk associated with extended anticoagulation in these patients necessitates caution, and prospective clinical studies are required to further investigate these findings.

Addendum

A.T. Cohen (Chair), H.R. Büller, L. Haskell, D. Hu, R. Hull, A. Mebazaa, G. Merli, S. Schellong, T.E. Spiro, A.C. Spyropoulos and V.F. Tapson formed the MAGELLAN Study Steering Committee and each provided substantial input into the design and conduct of the study, and analysis and interpretation of its results, including this *post-hoc* analysis. For this analysis, Y.H. DeSanctis and M. Homering performed the statistical analyses of data, and P. Burton contributed substantially to the design of this analysis and interpretation of the data. A.T. Cohen and T.E. Spiro were primarily responsible for critically reviewing and revising this manuscript, but all authors contributed to the revision of the intellectual content and approved the final version of the manuscript to be published.

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Disclosure of Conflicts of Interest

A.T. Cohen has undertaken consultancy work and received honoraria from Astellas, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, GSK, J&J, Mitsubishi Pharma, Pfizer, Portola, Sanofi and Schering Plough. He has also received research support from Merck as well as honoraria and consultancy for Takeda. A.T. Cohen has also undertaken scientific advisory work and speaker bureau work for Bayer, BMS, Daiichi Sankyo, J&J, Pfizer and Sanofi. He has undertaken scientific advisory board work for Portola and speaker bureau work for Boehringer Ingelheim. T.E. Spiro is a full-time employee of Bayer HealthCare. A.C. Spyropoulos has received consulting fees from Astellas, Boehringer Ingelheim, Bristol-Myers Squibb and J&J. Y.H. DeSanctis has confirmed no conflict of interest. M. Homering is also an employee of Bayer HealthCare; H.R. Büller has also received fees from Bayer. L. Haskell is an employee of Janssen Pharmaceuticals. D. Hu has confirmed that he has no conflict of interest. R. Hull has undertaken consultancy work for Bayer, Leo Pharma, Sanofi-Aventis, Pfizer, GSK, Wyeth Pharmaceuticals and Portola Pharmaceuticals. A. Mebazaa has worked as a Steering Committee consultant for Magellan. G. Merli has acted as a scientific consultant and received research support from BMS, J&J and Sanofi-Aventis. S. Schellong has acted as consultant for, and received speaker fees from, Bayer, Boehringer, Daiichi, BMS, Sanofi. Dr Schellong has also received speaker fees from GSK and Leo. V.F. Tapson has received consulting fees from Bayer, Bristol-Myers Squibb, Covidien and Sanofi along with lecture fees from Covidien and Sanofi. V.F. Tapson has also received payment for educational presentations from Sanofi and grant support through his institution from Bayer and Sanofi. P. Burton is an employee of J&J.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Appendices.
Fig. S1. Patients included in the analysis and reasons for exclusion.
Fig. S2. Distribution of D-dimer concentration ($\mu g\ mL^{-1}$) at baseline versus at Day 10 for patients with and without venous thromboembolism at Day 35.
Fig. S3. Receiver operating characteristic analysis for D-dimer at baseline by venous thromboembolism rate at Day 35.
Table S1. ROC analysis for venous thromboembolism at Day 10 (per-protocol population) and Day 35 (efficacy population) by baseline D-dimer group.
Table S2. Area under the receiver operating characteristic curve for D-dimer at baseline and other VTE risk scores.

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