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# Predicting the Risk of Venous Thromboembolism in Patients Hospitalized With Heart Failure

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***Background***—Whether heart failure (HF) increases the risk of venous thromboembolism (VTE) is not well established. In the phase III MAGELLAN (Multicenter, rAndomized, parallel Group Efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically iLL patients comparing rivaroxabAN with enoxaparin) trial, extended-duration rivaroxaban was compared with standard-duration enoxaparin followed by placebo for VTE prevention in 8101 hospitalized acutely ill patients with or without HF. The aim of this analysis was to evaluate the relationship between HF severity and the risk of VTE in MAGELLAN patients.

***Methods and Results***—Hospitalized patients diagnosed with HF were included according to New York Heart Association class III or IV at admission (n=2593). HF severity was determined by N-terminal probrain natriuretic peptide (NT-proBNP) plasma concentrations (median 1904 pg/mL). Baseline plasma D-dimer concentrations ranged from 0.6 to 1.7 µg/L for the less and more severe HF subgroups. Patients with more severe HF had a greater incidence of VTE versus patients with less severe HF, with a significant trend up to Day 10 (4.3% versus 2.2%; *P*=0.0108) and Day 35 (7.2% versus 4.1%; *P*=0.0150). Multivariable analysis confirmed that NT-proBNP concentration was associated with VTE risk up to Day 10 (*P*=0.017) and D-dimer concentration with VTE risk up to Day 35 (*P*=0.005). The association between VTE risk and HF severity that was observed in the enoxaparin/placebo group was not seen in the extended-duration rivaroxaban group.

***Conclusions***—Patients with more severe HF, as defined by high NT-proBNP plasma concentration, were at increased risk of VTE. NT-proBNP may be useful to identify high short-term risk, whereas elevated D-dimer may be suggestive of high midterm risk.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00571649.
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Heart failure (HF) is a common, costly, and potentially fatal syndrome. In developed countries, ≈2% of the adult population experiences HF; this rate increases to 6% to 10% in those aged ≥65 years.[1] Hospitalized HF is associated with an increased risk of venous thromboembolism (VTE) as a result of vascular abnormalities, increased coagulability, and impaired blood flow.[2] In the absence of thromboprophylaxis, the incidence of VTE has been reported to range from ≈4% to 26% in patients with decompensated HF.[3] A recent study showed that HF increases the near-term risk for pulmonary embolism not associated with diagnosed peripheral deep vein thrombosis.[4] In patients with pulmonary embolism, recurrent VTE and right ventricular dysfunction have both been associated with elevated levels of N-terminal probrain natriuretic peptide (NT-proBNP).[5,6] However, the relationship between HF severity and risk of VTE is not well established.

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Several clinical trials have demonstrated that the risk of VTE in patients with HF can be reduced with thromboprophylaxis,[7–10] and the American College of Chest Physicians clinical practice guidelines recommend the use of unfractionated heparin, low-molecular-weight heparin, or fondaparinux in acutely ill medical patients with HF at risk of thrombosis.[11] However, despite these guidelines, there is evidence that thromboprophylaxis is underused in this patient group, and there is uncertainty about which patients with HF should receive thromboprophylaxis.[12–15] An analysis of U.S. registry

data has shown that pharmacological VTE prophylaxis is provided to fewer than one-third of eligible patients hospitalized with New York Heart Association (NYHA) class III or IV HF.[16] Therefore, there is a need to identify patients with hospitalized HF who are at particularly high risk of VTE to facilitate the provision of optimal thromboprophylaxis.

MAGELLAN (Multicenter, rAndomized, parallel Group Efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically iLL patients comparing rivaroxabAN with enoxaparin) was a multicenter, randomized, double-blind phase III study in hospitalized, acutely ill patients, in which rivaroxaban (35±4 days) was compared with enoxaparin (10±4 days) followed by placebo. Approximately 32% of patients included in MAGELLAN were hospitalized for HF (NYHA class III or IV). In this subgroup, the rates of VTE were 5.0% in the rivaroxaban arm and 6.2% in the enoxaparin/placebo arm up to Day 35.[17]

The objective of this analysis was to evaluate the relationship between HF severity and VTE risk in hospitalized patients with HF included in the MAGELLAN study, and whether VTE risk was altered by either of the 2 VTE prophylaxis regimens.

## Methods

### Patients and Study Design

The study design of MAGELLAN and the inclusion and exclusion criteria have been reported previously.[18] In brief, patients who were aged ≥40 years and who were hospitalized for an acute medical illness with risk factors for VTE 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 study was approved by an institutional review committee, and all patients gave informed consent.

The primary efficacy end points were the composite 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 clinically relevant bleeding (the composite of treatment-emergent major bleeding and nonmajor clinically relevant bleeding up to Day 10 and Day 35). Major bleeding and laboratory parameters were secondary safety outcomes.[18]

The primary diagnosis was determined by the clinician. Patients diagnosed with HF were categorized by the clinician as having NYHA class III or NYHA class IV HF at admission. HF severity was determined using NYHA classification or NT-proBNP concentration.[19,20]

### Laboratory Parameters

In patients categorized as having HF, plasma was drawn at screening, Day 10, and Day 35, and stored at −80°C. Measurement of NT-proBNP concentration (pg/mL) was carried out subsequently by a central laboratory using an enzyme immunoassay for the quantitative determination of NT-proBNP levels (Biomedica, Vienna, Austria) as described previously.[21] Patients with HF were stratified into quartiles according to baseline NT-proBNP concentration (quartile 1, <765 pg/mL; quartile 2, 767–1904 pg/mL; quartile 3, 1906–5034 pg/mL; quartile 4, >5038 pg/mL) for comparative analysis of the primary efficacy, principal safety, and major bleeding outcomes. NT-proBNP concentrations were not measured in patients who were not hospitalized for HF.

In all patients, D-dimer concentration was determined at baseline, Day 10, and Day 35 using the STA-Liatest D-DI (Diagnostica Stago, Asnières-sur-Seine, France) assay (upper limit of normal 0.5 µg/mL). Prothrombin time (PT) was measured using the STA Neoplastine CI Plus assay (Diagnostica Stago). The prothrombinase-induced clotting time (PiCT) assay (Diagnostica Stago) was used to extrapolate rivaroxaban plasma concentration. PT and PiCT were measured at baseline, Day 1, Day 10, and Day 35.

### Statistical Analysis

Patients with HF were a predefined subgroup. Measurement of NT-proBNP and D-dimer concentration was planned for analytic purposes. A multivariable analysis of the primary efficacy end point for 2 prespecified time periods (Day 1–10 and Day 1–35; Day 1 being the day of randomization) was conducted in HF patients. The multivariable analysis included treatment group and NT-proBNP concentration at baseline, and applied a stepwise variable selection (using an entry level of 30%) for additional covariates. Analyses up to Day 10 and up to Day 35 were considered independently because of the differing durations of the enoxaparin and rivaroxaban treatment regimens used. Furthermore, different criteria were used to define valid analysis populations for Day 10 and Day 35.[18]

The incidence rates of the primary efficacy, principal safety, and major bleeding outcomes for non-HF and HF patients in each treatment group were reported. The relative risk and the corresponding nonstratified asymptotic 2-sided 95% confidence intervals for HF patients (quartile 4) versus non-HF patients were calculated. A trend test for the primary efficacy end point and bleeding outcomes by NT-proBNP quartile group was conducted and *P* values were calculated using the Cochran–Armitage trend test.

Cumulative rates of symptomatic VTE and cardiovascular death up to Day 90+7 were analyzed for non-HF patients and for HF patients by NT-proBNP quartile using a Kaplan–Meier curve for the cumulative event rate for each quartile group. A log-rank test was used to compare the distribution between quartiles 1 and 4 and to calculate *P* values for differences between quartiles.

Cumulative rates and bleeding outcomes up to Day 10 and Day 35 were recorded in the safety population, which included all patients who had received at least 1 dose of study medication. All other analyses were performed in the modified intention-to-treat population, which included patients valid for the safety population who had an adequate assessment of VTE.

## Results

### Patients

A total of 8101 patients were randomized in the MAGELLAN study. Of the 7998 patients included in the safety population, 2593 (32%) were diagnosed with HF; 1773 patients had NYHA class III HF and 820 had NYHA class IV HF at admission. Measurements of NT-proBNP were available for analysis in 2327 patients with HF. The median NT-proBNP concentration was 1904 pg/mL.

Patient characteristics are summarized in Tables 1 through 3. History of atrial fibrillation, hypertension, and coronary artery disease occurred at a higher incidence in patients with HF than in those without HF. Ischemic cardiomyopathy was the most frequent cause of HF in the index hospitalization, followed by hypertensive cardiomyopathy (Table 1). Patients with HF had more comedication use with β-blocking agents, angiotensin-converting enzyme inhibitors, or organic nitrates used for the treatment of this condition (Table 2). The highest NT-proBNP levels were associated with more severe renal impairment (Table 3).

### Heart Failure Severity and Venous Thromboembolic Risk

Up to both Day 10 and Day 35, the primary efficacy end point occurred more frequently in HF patients with NT-proBNP concentrations greater than the median of 1904 pg/mL (ie, quartiles 3 and 4) than in HF patients with lower NT-proBNP

**Table 1.    Demographic and Baseline Characteristics for Non-HF and HF Patients by Baseline NT-proBNP Quartile and Characteristics of HF at Admission by Baseline NT-proBNP Quartile**

| NT-proBNP range (n) | Non-HF Patients | HF Patients | | | |
|---|---|---|---|---|---|
| | N/A (5405) | Quartile 1 <765 pg/mL (582) | Quartile 2 767 to 1904 pg/mL (582) | Quartile 3 1906 to 5034 pg/mL (582) | Quartile 4 >5038 pg/mL (581) |
| Male sex, n (%) | 2877 (53.2) | 300 (51.5) | 307 (52.7) | 331 (56.9) | 348 (59.9) |
| White race, n (%) | 3653 (67.6) | 420 (72.2) | 403 (69.2) | 405 (69.6) | 411 (70.7) |
| Age, mean (SD), years | 68.5 (12.0) | 69.5 (10.6) | 70.0 (11.2) | 71.0 (11.2) | 72.0 (11.5) |
| Weight, mean (SD), kg | 76.1 (21.8) | 83.9 (22.8) | 82.7 (23.6) | 78.9 (19.8) | 74.3 (18.5) |
| Disease history, n (%) | | | | | |
|   Atrial fibrillation* | 338 (6.3) | 107 (18.4) | 164 (28.2) | 222 (38.1) | 181 (31.2) |
|   Diabetes mellitus | 838 (15.5) | 99 (17.0) | 91 (15.6) | 105 (18.0) | 95 (16.4) |
|   Chronic obstructive pulmonary disease | 1526 (28.2) | 159 (27.3) | 124 (21.3) | 109 (18.7) | 105 (18.1) |
|   Hypertension | 3459 (64.0) | 442 (75.9) | 425 (73.0) | 416 (71.5) | 398 (68.5) |
|   Coronary artery disease | 462 (8.5) | 157 (27.0) | 165 (28.4) | 203 (34.9) | 175 (30.1) |
| Primary cause/causes of the index hospitalized HF, n (%) | | | | | |
|   Ischemic | N/A | 284 (48.8) | 237 (40.7) | 312 (53.6) | 289 (49.7) |
|   Hypertensive | N/A | 156 (26.8) | 152 (26.1) | 88 (15.1) | 96 (16.5) |
|   Valvular | N/A | 15 (2.6) | 21 (3.6) | 35 (6.0) | 38 (6.5) |
|   Alcohol | N/A | 2 (0.3) | 7 (1.2) | 5 (0.9) | 5 (0.9) |
|   Idiopathic dilated | N/A | 20 (3.4) | 34 (5.8) | 44 (7.6) | 48 (8.3) |
|   Viral | N/A | 1 (0.2) | 0 | 2 (0.3) | 1 (0.2) |
|   Congenital anomaly | N/A | 1 (0.2) | 1 (0.2) | 2 (0.3) | 1 (0.2) |
|   Unknown | N/A | 60 (10.3) | 95 (16.3) | 76 (13.1) | 77 (13.3) |
|   Other | N/A | 43 (7.4) | 35 (6.0) | 18 (3.1) | 26 (4.5) |
| Ejection fraction, mean (SD), % | N/A | 47.4 (12.8) | 42.6 (14.3) | 37.3 (14.0) | 34.1 (12.1) |
| NYHA classification at admission, n (%) | | | | | |
|   III | N/A | 463 (79.6) | 415 (71.3) | 380 (65.3) | 321 (55.2) |
|   IV | N/A | 119 (20.4) | 167 (28.7) | 202 (34.7) | 260 (44.8) |

HF indicates heart failure; N/A, not applicable; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association; and SD, standard deviation.
*Of note, patients with atrial fibrillation were not previously treated with anticoagulant.

concentrations (ie, quartiles 1 and 2), or in patients without HF (Table 4). Overall, there was a significant trend for an association between VTE risk and NT-proBNP concentration at both time points ($P$=0.0108 up to Day 10 and $P$=0.0150 up to Day 35). Up to Day 10, the relative risk of the primary efficacy end point was significantly higher for HF patients in the third quartile of NT-proBNP than for non-HF patients (Figure 1A); the same was true up to Day 35 for HF patients in the fourth quartile of NT-proBNP compared with non-HF patients (Figure 1B).

The higher incidence of VTE observed in HF patients with high NT-proBNP correlates with a higher concentration of D-dimer at baseline (Table 3), Day 10, and Day 35 (Figure 2). D-dimer concentrations in quartiles 3 and 4 of NT-proBNP remained higher than those observed in non-HF patients or those in HF quartiles 1 and 2, at each time point.

The multivariable analysis in hospitalized HF patients indicated that NT-proBNP level was associated with VTE risk up to Day 10 ($P$=0.0173) but not up to Day 35 ($P$=0.8208; Table 5). The multivariable analysis also identified D-dimer ($P$=0.0047) and baseline high sensitivity C-reactive

protein ($P$=0.5329) as being associated with VTE risk up to Day 35. Treatment group, body mass index, and creatinine clearance were not associated with VTE risk at either time point (Table 5).

In the HF group, incidence rates for the primary efficacy end point up to Day 10 and Day 35 were, however, similar when the severity of HF was classified as NYHA class III and class IV (Table 6).

**Cumulative Incidence of Symptomatic Venous Thromboembolism and Cardiovascular Death**
The Kaplan–Meier curve of symptomatic VTE indicates that, from an early time point, HF patients with the highest NT-proBNP levels (quartile 4) are at increased risk compared with those in quartile 1 and that this risk continues to increase over time ($P$=0.0248 for difference in cumulative incidence; Figure 3A). Likewise, the cumulative incidence of cardiovascular death increases more rapidly in NT-proBNP quartile 4 compared with quartile 1 ($P$<0.001 for difference in cumulative incidence; Figure 3B).

**Table 2.    Concomitant Medications for Non-HF and HF Patients by Baseline NT-proBNP Quartile**

| NT-proBNP range (n) | Non-HF Patients N/A (5405) | HF Patients | | | |
|---|---|---|---|---|---|
| | | Quartile 1 <765 pg/mL (582) | Quartile 2 767 to 1904 pg/mL (582) | Quartile 3 1906 to 5034 pg/mL (582) | Quartile 4 >5038 pg/mL (581) |
| Concomitant medication taken before initiation of study medication, n (%) | | | | | |
| β-blocking agents | 1063 (19.7) | 288 (49.5) | 328 (56.4) | 345 (59.3) | 335 (57.7) |
| ACE inhibitors* | 1649 (30.5) | 369 (63.4) | 350 (60.1) | 339 (58.2) | 348 (59.9) |
| Angiotensin receptor blockers* | 763 (14.1) | 122 (20.9) | 125 (21.5) | 113 (19.4) | 92 (15.8) |
| Organic nitrates | 458 (8.5) | 230 (39.5) | 234 (40.2) | 234 (40.2) | 208 (35.8) |
| Acetylsalicylic acid | 1714 (31.7) | 277 (47.6) | 305 (52.4) | 320 (55.0) | 291 (50.1) |
| Loop diuretics | 1093 (20.2) | 415 (71.3) | 463 (79.6) | 497 (85.4) | 505 (86.9) |
| Thiazide diuretics | 267 (4.9) | 41 (7.0) | 37 (6.4) | 33 (5.7) | 29 (5.0) |
| Aldosterone antagonists | 222 (4.1) | 189 (32.5) | 233 (40.0) | 237 (40.7) | 290 (49.9) |

ACE indicates angiotensin-converting enzyme; HF, heart failure; N/A, not applicable; and NT-proBNP, N-terminal probrain natriuretic peptide.

*Alone and in combination with other drugs of the same class.

## Heart Failure Severity and Risk of Bleeding

Up to both Day 10 and Day 35, there was a numeric increase in clinically relevant bleeding as NT-proBNP concentration increased (Table 7). Major bleeding occurred at a low rate in patients without HF and across HF quartiles (Table 7) both up to Day 10 and Day 35. No significant trend was observed between NT-proBNP concentration and the risk of clinically relevant bleeding or major bleeding. Similar results were seen in both treatment arms, although the incidence of clinically relevant bleeding was higher in the rivaroxaban group than in the enoxaparin/placebo group at both time points (Table 7).

The relative risk of clinically relevant bleeding was significantly higher up to Day 10 for HF patients with the highest NT-proBNP compared with non-HF patients. No significant difference was seen up to Day 35 (Figure 4A and 4B).

## Treatment Differences

In patients with severe HF with high NT-proBNP or NYHA class IV, the incidence rates of the primary efficacy end point

**Table 3.    Laboratory Results for Non-HF and HF Patients by Baseline NT-proBNP Quartile**

| NT-proBNP range (n) | Non-HF Patients N/A (5405) | HF Patients | | | |
|---|---|---|---|---|---|
| | | Quartile 1 <765 pg/mL (582) | Quartile 2 767 to 1904 pg/mL (582) | Quartile 3 1906 to 5034 pg/mL (582) | Quartile 4 >5038 pg/mL (581) |
| Creatinine clearance, n (%) | | | | | |
| <30 mL/min | 75 (1.4) | 6 (1.0) | 10 (1.7) | 14 (2.4) | 31 (5.3) |
| 30–<50 mL/min | 845 (15.6) | 101 (17.4) | 134 (23.0) | 179 (30.8) | 248 (42.7) |
| 50–≤80 mL/min | 1971 (36.5) | 245 (42.1) | 236 (40.5) | 234 (40.2) | 239 (41.1) |
| >80 mL/min | 2402 (44.4) | 227 (39.0) | 194 (33.3) | 147 (25.3) | 55 (9.5) |
| NT-proBNP concentration, median [IQR], pg/mL | N/A | 496.4 [304.2] | 1032.8 [442.7] | 3118.0 [1505.9] | 8699.3 [5886.7] |
| Baseline D-dimer concentration: median, µg/mL (n) | 0.9 (5100) | 0.6 (560) | 0.9 (569) | 1.2 (559) | 1.7 (557) |
| Rivaroxaban plasma concentration: median, µg/L (n) | | | | | |
| Day 1 peak | 168.9 (2119) | 171.7 (248) | 162.1 (247) | 189.7 (244) | 171.8 (247) |
| Day 10 trough/peak | 13.1 (2049)/ 174.5 (1925) | 15.8 (253)/ 179.9 (237) | 21.7 (252)/ 204.6 (236) | 24.0 (240)/ 201.8 (225) | 23.9 (221)/ 209.1 (199) |
| Day 35 peak | 165.4 (544) | 161.1 (64) | 140.2 (67) | 169.3 (58) | 150.8 (44) |
| Rivaroxaban PT: median, s (n) | | | | | |
| Baseline | 14.2 (2304) | 14.0 (255) | 14.5 (254) | 14.8 (253) | 15.4 (248) |
| Day 1 peak | 19.0 (2255) | 19.0 (254) | 19.3 (254) | 20.7 (250) | 21.8 (261) |
| Day 10 trough/peak | 14.4 (2077)/ 18.8 (1958) | 14.6 (252)/ 19.0 (245) | 15.1 (248)/ 20.4 (241) | 15.4 (225)/ 20.6 (227) | 15.6 (220)/ 21.3 (208) |
| Day 35 peak | 18.4 (557) | 19.0 (59) | 18.1 (68) | 19.5 (58) | 19.1 (45) |

HF indicates heart failure; IQR, interquartile range; N/A, not applicable; NT-proBNP, N-terminal probrain natriuretic peptide; and PT, prothrombin time.

**Table 4. Incidence Rates for the Primary Efficacy End Point Up to Day 10 and Day 35 for Patients With or Without Heart Failure, and Trend Test by Baseline NT-proBNP Quartile***

| Treatment Group | Non-HF Patients | HF Patients | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| NT-proBNP range (n) | N/A (5405) | Quartile 1 <765 pg/mL (582) | Quartile 2 767 to 1904 pg/mL (582) | Quartile 3 1906 to 5034 pg/mL (582) | Quartile 4 >5038 pg/mL (581) | *P* Value for Trend Test by NT-proBNP Quartile (2-Sided)* |
| Day 10, n/N (%) | | | | | | |
| Overall | 123/4351 (2.8) | 11/492 (2.2) | 10/500 (2.0) | 26/478 (5.4) | 21/487 (4.3) | 0.0108 |
| Enoxaparin | 61/2192 (2.8) | 4/241 (1.7) | 4/249 (1.6) | 15/227 (6.6) | 13/248 (5.2) | 0.0060 |
| Rivaroxaban | 62/2159 (2.9) | 7/251 (2.8) | 6/251 (2.4) | 11/251 (4.4) | 8/239 (3.3) | 0.3992 |
| Day 35, n/N (%) | | | | | | |
| Overall | 194/4026 (4.8) | 19/465 (4.1) | 21/462 (4.5) | 31/446 (7.0) | 32/443 (7.2) | 0.0150 |
| Enoxaparin/placebo | 112/2043 (5.5) | 9/236 (3.8) | 10/232 (4.3) | 20/220 (9.1) | 19/222 (8.6) | 0.0305 |
| Rivaroxaban | 82/1983 (4.1) | 10/229 (4.4) | 11/230 (4.8) | 11/226 (4.9) | 13/221 (5.9) | 0.2116 |

HF indicates heart failure; N/A, not applicable; and NT-proBNP, N-terminal probrain natriuretic peptide.
*Restricted to patients with heart failure.

were lower in the rivaroxaban group than in the enoxaparin/placebo group (Tables 4 and 6, respectively). Up to both Day 10 and Day 35, there was an association between VTE risk and NT-proBNP concentration in the enoxaparin/placebo group (*P*=0.0060 and *P*=0.0305, respectively) but not in the rivaroxaban

group at either time point (Table 4). Likewise, in the enoxaparin/placebo group, the relative risk of VTE was significantly higher for HF patients in quartiles 3 and 4 up to Day 10 and quartile 3 up to Day 35 (included the placebo-only phase) compared with non-HF patients (Figure 1A and 1B), whereas no differences in the relative risk of VTE were seen in the rivaroxaban group between HF and non-HF patients at either time point (Figure 1A and 1B).

D-dimer levels were also lower, although not significantly, in HF patients with the highest NT-proBNP levels in the rivaroxaban group compared with the enoxaparin/placebo group up to Day 35 (included the placebo-only phase; Figure 2B).

Of note, rivaroxaban plasma concentrations, extrapolated using the PiCT assay, were not affected by the presence or severity of HF, but there was a trend toward prolonged PT as severity increased (Table 3).
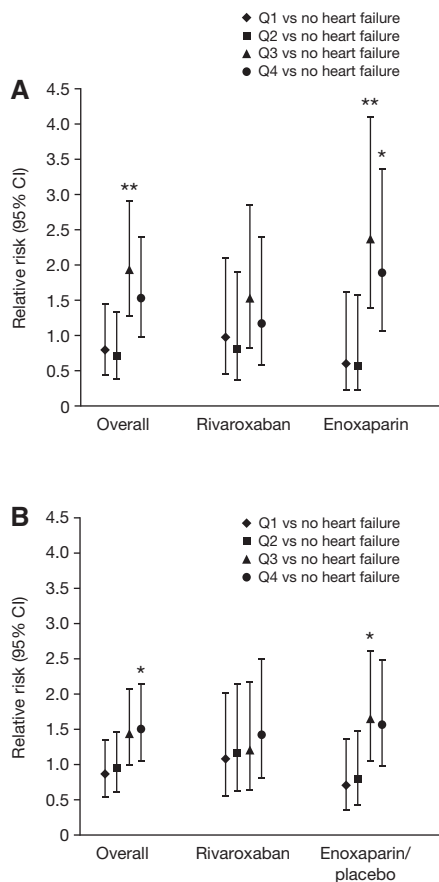


**Figure 1.** Relative risk of the primary efficacy end point for heart failure (HF) patients by N-terminal probrain natriuretic peptide quartile (Q1, Q2, Q3, and Q4) vs non-HF patients up to Day 10 (**A**) and up to Day 35 (**B**). CI indicates confidence interval. *P<0.05; **P<0.01.
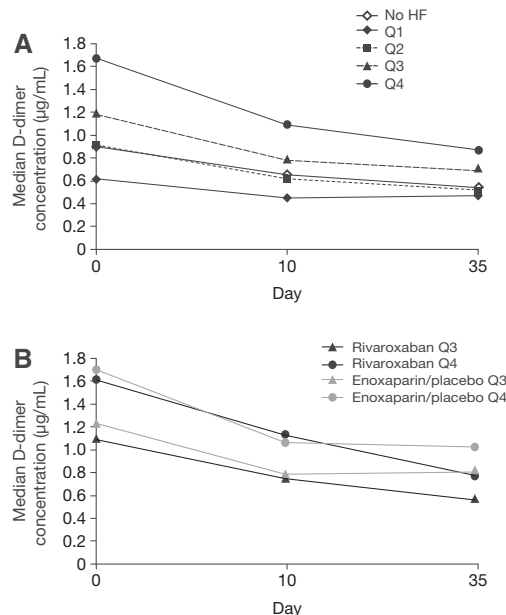


**Figure 2.** Median D-dimer concentration over time for non–heart failure (HF) and HF patients by N-terminal probrain natriuretic peptide quartile in the overall population (**A**) and by treatment arm (**B**).

**Table 5.     Multivariable Analysis of the Primary Efficacy End Point Up to Day 10 and Day 35**

| Covariate | Comparison for Odds Ratio | Odds Ratio | 95% CI | P Value |
|---|---|---|---|---|
| Up to Day 10 | | | | |
| Treatment group | Rivaroxaban versus enoxaparin | 0.86 | 0.52 to 1.41 | 0.547 |
| NT-proBNP | Quartile 2 versus Quartile 1 | 0.51 | 0.23 to 1.09 | 0.017 |
| | Quartile 3 versus Quartile 1 | 0.45 | 0.21 to 0.99 | |
| | Quartile 4 versus Quartile 1 | 1.21 | 0.65 to 2.23 | |
| Body mass index, kg/m$^2$ | <18.5 versus 18.5–<25 | 2.37 | 0.77 to 7.32 | 0.446 |
| | 25–<30 versus 18.5–<25 | 1.27 | 0.69 to 2.35 | |
| | 30–<35 versus 18.5–<25 | 0.66 | 0.28 to 1.55 | |
| | 35–<40 versus 18.5–<25 | 0.95 | 0.33 to 2.72 | |
| | ≥40 versus 18.5–<25 | 1.11 | 0.34 to 3.67 | |
| Creatinine clearance, ml/min | <30 versus >80 | 0.72 | 0.09 to 5.98 | 0.935 |
| | 30–<50 versus >80 | 0.95 | 0.43 to 2.08 | |
| | 50–≤80 versus >80 | 1.11 | 0.56 to 2.20 | |
| Up to Day 35 | | | | |
| Treatment group | Rivaroxaban versus enoxaparin | 0.77 | 0.51 to 1.15 | 0.201 |
| NT-proBNP | Quartile 2 versus Quartile 1 | 0.88 | 0.47 to 1.64 | 0.821 |
| | Quartile 3 versus Quartile 1 | 0.83 | 0.46 to 1.50 | |
| | Quartile 4 versus Quartile 1 | 1.08 | 0.63 to 1.84 | |
| Body mass index, kg/m$^2$ | <18.5 versus 18.5–<25 | 1.88 | 0.69 to 5.18 | 0.732 |
| | 25–<30 versus 18.5–<25 | 1.00 | 0.61 to 1.66 | |
| | 30–<35 versus 18.5–<25 | 0.74 | 0.39 to 1.42 | |
| | 35–<40 versus 18.5–<25 | 0.83 | 0.36 to 1.94 | |
| | ≥40 versus 18.5–<25 | 0.96 | 0.36 to 2.60 | |
| Baseline hs-CRP | > median versus ≤ median | 1.54 | 1.02 to 2.34 | 0.042 |
| Creatinine clearance, ml/min | <30 versus >80 | 0.90 | 0.19 to 4.23 | 0.533 |
| | 30–<50 versus >80 | 1.48 | 0.77 to 2.85 | |
| | 50–≤80 versus >80 | 1.10 | 0.60 to 2.03 | |
| D-dimer | >2×ULN versus ≤2×ULN | 1.89 | 1.20 to 2.96 | 0.005 |

CI indicates confidence interval; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal probrain natriuretic peptide; and ULN, upper limit of normal.

## Discussion

In this analysis of 2593 hospitalized HF patients, we observed an association between HF severity and both VTE risk and D-dimer concentration up to Day 10 and Day 35. Multivariable

**Table 6.     Incidence Rates for the Primary Efficacy End Point Up to Day 10 and Day 35 for Patients With NYHA III or NYHA IV Heart Failure**

| Treatment Group Baseline NT-proBNP median, pg/mL | NYHA III 1386 | NYHA IV 3056 |
|---|---|---|
| Up to Day 10, n/N (%) | | |
| Overall | 51/1481 (3.4) | 24/671 (3.6) |
| Enoxaparin | 24/743 (3.2) | 15/336 (4.5) |
| Rivaroxaban | 27/738 (3.7) | 9/335 (2.7) |
| Up to Day 35, n/N (%) | | |
| Overall | 77/1388 (5.5) | 35/610 (5.7) |
| Enoxaparin/placebo | 42/705 (6.0) | 21/309 (6.8) |
| Rivaroxaban | 35/683 (5.1) | 14/301 (4.7) |

NT-proBNP indicates N-terminal probrain natriuretic peptide; and NYHA, New York Heart Association.

analysis confirmed NT-proBNP concentration to be a significant predictor of VTE risk up to Day 10 but not up to Day 35 in HF patients. These findings provide the first evidence of a significant correlation between the risk of VTE and HF severity, as determined by NT-proBNP concentration. In patients with acute pulmonary embolism, studies have shown elevated NT-proBNP to be an independent predictor of recurrent VTE and to correlate with adverse clinical outcomes and mortality.[5,6] Conversely, in a study of data from the Acute Decompensated Heart Failure National Registry, which included HF patients aged ≥65 years, higher BNP levels were not associated with an increase in the risk of thromboembolism.[22]

In the current analysis, the risk of VTE in the overall group was higher in patients with more severe HF (NT-proBNP concentration ≥1906 pg/mL) than in those without HF or with less severe disease. These findings suggest that NT-proBNP could be used as a simple measure to identify patients with HF who are at high risk of thromboembolism and should, therefore, be considered for VTE prophylaxis. This result is consistent with recent literature suggesting that venous congestion, rather than low cardiac output, is a major determinant
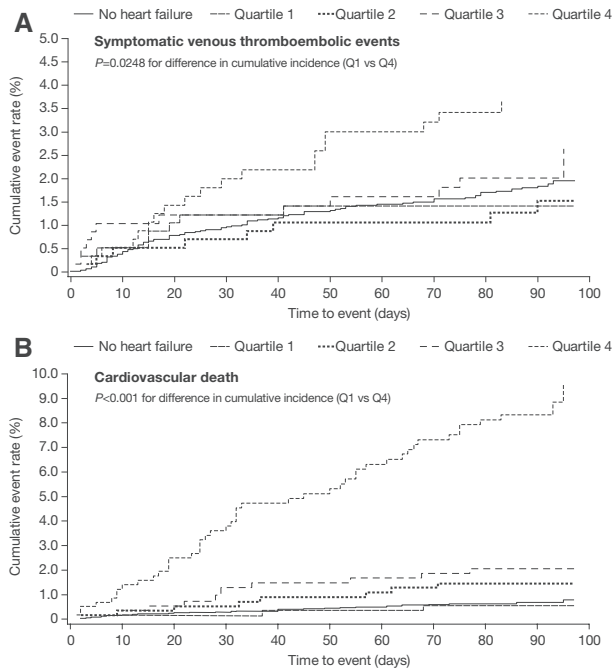
**Figure 3.** Cumulative rates (Kaplan–Meier) of events: symptomatic venous thromboembolic events (**A**) and cardiovascular death (**B**).

of organ dysfunction.[23–25] NYHA class, another indicator of HF severity, had little or no effect on the incidence of VTE, suggesting that NT-proBNP is a better predictor of thromboembolic risk.

A positive correlation was seen between NT-proBNP concentration and D-dimer concentration, another marker that has recently been shown to predict VTE risk in acutely ill medical patients.[26] This difference was most marked for the patients with more severe HF, who had noticeably higher D-dimer levels than patients without HF at each time point tested. The Kaplan–Meier curves of symptomatic VTE and cardiovascular death further support the finding that patients with severe HF are a high-risk group. For both symptomatic venous thromboembolic events and cardiovascular death, the curve for the highest NT-proBNP concentrations separates early from the curve for the quartile 1 HF group and the cumulative rate continues to increase throughout the study duration (up to Day 90+7). Data from the Acute Decompensated Heart Failure National Registry support these findings; each 30% increase in BNP was associated with an increased risk of death and myocardial infarction.[22]

No relationship was observed between HF severity and clinically relevant bleeding or major bleeding. However, clinically relevant bleeding did occur more frequently as NT-proBNP concentration increased, and the risk of bleeding was higher in patients with the most severe HF than in patients without HF up to Day 10. It is possible that the increase in risk of bleeding could be a result of other patient factors, such as decreased renal function or concomitant medications.

The significant association between VTE risk and HF severity that was observed in the overall and enoxaparin/placebo groups was not seen in the extended-duration rivaroxaban group, suggesting that rivaroxaban may reduce the risk of VTE in patients with more severe HF. This finding is

**Table 7. Incidence Rates for Clinically Relevant Bleeding and Major Bleeding Up to Day 10 and Day 35 for Patients With or Without Heart Failure, and Trend Test by Baseline NT-proBNP Quartile***

| Treatment Group | Non-HF Patients | HF Patients | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| NT-proBNP range (n) | N/A (5405) | Quartile 1 <765 pg/mL (582) | Quartile 2 767 to 1904 pg/mL (582) | Quartile 3 1906 to 5034 pg/mL (582) | Quartile 4 >5038 pg/mL (581) | P Value for Trend Test by NT-proBNP Quartile (2-Sided)* |
| Clinically relevant bleeding† | | | | | | |
| Up to Day 10, n/N (%) | | | | | | |
| Overall | 108/5405 (2.0) | 5/582 (0.9) | 6/582 (1.0) | 14/582 (2.4) | 19/581 (3.3) | 0.1929 |
| Enoxaparin | 33/2700 (1.2) | 2/293 (0.7) | 2/291 (0.7) | 4/290 (1.4) | 5/286 (1.7) | 0.6827 |
| Rivaroxaban | 75/2705 (2.8) | 3/289 (1.0) | 4/291 (1.4) | 10/292 (3.4) | 14/295 (4.7) | 0.2028 |
| Up to Day 35, n/N (%) | | | | | | |
| Overall | 153/5405 (2.8) | 10/582 (1.7) | 14/582 (2.4) | 20/582 (3.4) | 22/581 (3.8) | 0.2621 |
| Enoxaparin/placebo | 46/2700 (1.7) | 2/293 (0.7) | 5/291 (1.7) | 5/290 (1.7) | 6/286 (2.1) | 0.7630 |
| Rivaroxaban | 107/2705 (4.0) | 8/289 (2.8) | 9/291 (3.1) | 15/292 (5.1) | 16/295 (5.4) | 0.2625 |
| Major bleeding | | | | | | |
| Up to Day 10, n/N (%) | | | | | | |
| Overall | 25/5405 (0.5) | 1/582 (0.2) | 1/582 (0.2) | 3/582 (0.5) | 2/581 (0.3) | 0.5792 |
| Enoxaparin | 7/2700 (0.3) | 0 | 1/291 (0.3) | 2/290 (0.7) | 0 | 0.8997 |
| Rivaroxaban | 18/2705 (0.7) | 1/289 (0.3) | 0 | 1/292 (0.3) | 2/295 (0.7) | 0.4478 |
| Up to Day 35, n/N (%) | | | | | | |
| Overall | 40/5405 (0.7) | 3/582 (0.5) | 2/582 (0.3) | 5/582 (0.9) | 3/581 (0.5) | 0.5340 |
| Enoxaparin/placebo | 10/2700 (0.4) | 0 | 1/291 (0.3) | 3/290 (1.0) | 0 | 0.9141 |
| Rivaroxaban | 30/2705 (1.1) | 3/289 (1.0) | 1/291 (0.3) | 2/292 (0.7) | 3/295 (1.0) | 0.4239 |

HF indicates heart failure; and NT-proBNP, N-terminal probrain natriuretic peptide.

*Restricted to patients with heart failure.

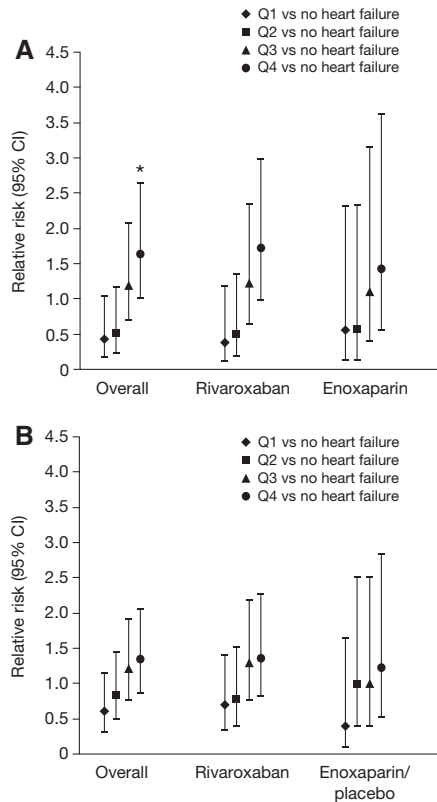†Major or nonmajor clinically relevant bleeding.

**Figure 4.** Relative risk of clinically relevant bleeding (major and nonmajor clinically relevant bleeding) for heart failure (HF) patients by quartile (Q1, Q2, Q3, and Q4) vs non-HF patients up to Day 10 (**A**) and up to Day 35 (**B**). CI indicates confidence interval. *$P<0.05$.

supported by the lower levels of D-dimer concentration with rivaroxaban compared with enoxaparin/placebo in patients with severe HF; however, the incidence of clinically relevant bleeding with rivaroxaban was higher across all quartiles

This analysis has some limitations. Although HF was a predefined subgroup, the analysis periods were predefined, and the measurement of NT-proBNP was planned for analytic purposes, the details of this specific analysis were not prespecified. Given the exploratory nature of these analyses, no adjustments to significance levels were made to account for multiple comparisons of the same data or for multiple efficacy variables or subgroups. Therefore, the results and reported *P* values should be interpreted with caution. Secondly, the diagnosis and classification of HF by NYHA class were determined by the treating physician and were not confirmed independently. Finally, NT-proBNP concentration may be influenced by factors other than heart disease, such as diabetes mellitus[27,28] or body weight,[27,28] but no adjustment was made for such confounding factors.

The current findings provide new evidence that patients with severe HF have a higher risk of VTE than those with less severe or no HF. Importantly, NT-proBNP may be more useful than NYHA class to identify patients at high short-term risk, whereas elevated D-dimer may be suggestive of high midterm risk.

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## Disclosures

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## CLINICAL PERSPECTIVE

Heart failure (HF) is common, costly, and potentially fatal. HF is also thought to increase the risk of venous thromboembolism (VTE) but the relationship between HF severity and VTE risk is not well established. In the randomized, double-blind phase III MAGELLAN study, hospitalized, acutely ill patients received thromboprophylaxis with either rivaroxaban (35±4 days) or enoxaparin (10±4 days) followed by placebo until Day 35. Approximately 32% of patients in MAGELLAN had HF. The aim of this analysis was to evaluate the relationship between HF severity and VTE risk in MAGELLAN, and whether VTE risk was altered by the two thromboprophylaxis regimens. An association between HF severity and VTE risk up to Day 10 and Day 35 was observed, but there was no relationship between HF severity and clinically relevant bleeding or major bleeding. The association between VTE risk and HF severity was observed with enoxaparin/placebo but not extended-duration rivaroxaban, suggesting that rivaroxaban may reduce VTE risk in patients with more severe HF. N-terminal probrain natriuretic peptide concentration was a significant predictor of VTE risk up to Day 10 (but not up to Day 35) in HF patients — the first evidence of such a correlation — and D-dimer concentration correlated with VTE risk up to Day 35. Although further investigation is required, these simple assays could potentially be used as surrogate markers to evaluate the short- and mid-term risks of VTE in HF patients.