Use of Prestudy Heparin Did Not Influence the Efficacy and Safety of Rivaroxaban in Patients Treated for Symptomatic Venous Thromboembolism in the EINSTEIN DVT and EINSTEIN PE Studies

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Abstract

Objectives: In the EINSTEIN DVT and EINSTEIN PE studies, the majority of patients received heparins to bridge the period during venous thromboembolism (VTE) diagnosis confirmation and the start of the study. In contrast to vitamin K antagonists (VKAs), rivaroxaban may not require initial heparin treatment.

Methods: To evaluate the effect of prestudy heparin on the efficacy and safety of rivaroxaban relative to enoxaparin/VKA, the 3-month incidence of recurrent VTE, the 14-day incidence of major and nonmajor clinically relevant bleeding were compared in patients who did and did not receive prestudy heparin.

Results: Of the 8,281 patients randomized, 6,937 (83.8%) received prestudy heparin (mean ± SD duration = rivaroxaban: 1.04 ± 0.74 days; enoxaparin 1.03 ± 0.42 days), and 1,344 (16.2%) did not. In patients who did not receive prestudy heparin, the incidences of recurrent VTE were similar in rivaroxaban (15 of 649, 2.3%) and enoxaparin/VKA (13 of 695, 1.9%) patients (adjusted hazard ratio [HR] = 1.11; 95% confidence interval [CI] = 0.52 to 2.37). The incidences of recurrent VTE were also similar in rivaroxaban (54 of 3,501, 1.5%) and enoxaparin/VKA (69 of 3,436, 2.0%) patients who did receive prestudy heparin (adjusted HR = 0.74; 95% CI = 0.52 to 1.06; pinteraction = 0.32). The incidences of major or nonmajor clinically relevant bleeding with rivaroxaban were not significantly different from those with enoxaparin/VKA, either with (105 of 3,485, 3.0% vs. 104 of 3,428, 3.0%; adjusted HR = 0.98; 95% CI = 0.75 to 1.29) or without (24 of 645, 3.7% vs. 30 of 688, 4.4%; adjusted HR = 0.81; 95% CI = 0.46 to 1.40; pinteraction = 0.68) prestudy heparin.
Conclusions: Although the majority of patients in the EINSTEIN studies received prestudy heparin, there were no notable differences in treatment effect of rivaroxaban versus enoxaparin/VKA in those who did and did not receive it. ACADEMIC EMERGENCY MEDICINE 2015;22:143–149 © 2015 The Authors. Academic Emergency Medicine published by Wiley Periodicals, Inc. on behalf of Society for Academic Emergency Medicine.

Rivaroxaban is an oral factor Xa inhibitor that has a peak anticoagulant effect within 2 to 4 hours after dosing and predictable pharmacokinetic and pharmacodynamic properties that obviate the need for routine anticoagulation laboratory monitoring.1,2 Rivaroxaban has been shown to be associated with a dose-dependent inhibition of factor Xa activity across all doses investigated,1–4 and maximum inhibition did not vary significantly between initial and steady-state administration.2 The onset of action of rivaroxaban is as rapid as that of low-molecular-weight heparins (LMWHs).5 Consequently, rivaroxaban has been evaluated in phase III studies as a fixed-dose monotherapy without an initial course of heparin for the treatment of acute symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), or both.6,7

In patients with symptomatic venous thromboembolism (VTE), an initial course of therapeutic heparin for at least 5 days is required to cover the slow onset of action of vitamin K antagonist (VKA) therapy.5 Patients who do not reach therapeutic levels of anticoagulation within 48 hours of commencing heparin show an increased risk of recurrent VTE (relative risk of 4.5).9 At 3 months, the incidence of recurrent VTE has been shown to range between 16 and 25% in patients not receiving initial heparin and those who receive inadequate heparin doses.9,13

In the EINSTEIN DVT and EINSTEIN PE studies,6,7,14 patients with confirmed acute symptomatic DVT and/or PE were treated with the combination of body weight-adjusted enoxaparin overlapping with and followed by a VKA (international normalized ratio [INR] = 2.0 to 3.0) or fixed-dose rivaroxaban given as a single-drug treatment. The results of a pooled analysis of these studies, encompassing over 8,000 patients, showed that rivaroxaban was noninferior to enoxaparin/VKA therapy and was associated with a substantial reduction in the occurrence of major bleeding.14

Patients were eligible for inclusion in the EINSTEIN studies if prestudy use of therapeutic doses of unfractionated heparin (UFH), LMWH, or fondaparinux did not exceed 48 hours. The reasons for allowing this time window were the frequent use of heparins in patients with suspected VTE by family practitioners before admittance to hospital, use in many hospitals during diagnostic workup, and to bridge the period in which patient participation in the study was being confirmed. Indeed, the latest international guidelines released by the American College of Chest Physicians recommend treatment with parenteral anticoagulants in patients with a high clinical suspicion of acute VTE while awaiting the results of diagnostic tests and even in patients with intermediate clinical suspicion, if diagnostic results are expected to be delayed for more than 4 hours.5 This is particularly relevant for patients with intermediate-risk PE, because of the substantial risk of early mortality (3% to 15%) in this group, when managed without prompt anticoagulation.15 Not surprisingly, many patients recruited in the EINSTEIN studies received short-term prestudy heparin. In this post hoc analysis of the EINSTEIN DVT and EINSTEIN PE studies, we report on the incidence of recurrent VTE and bleeding in patients receiving rivaroxaban compared with enoxaparin/VKA in relation to the use of heparin before randomization in the study.

METHODS

Study Design

This was a retrospective, post hoc analysis of data collected in the EINSTEIN DVT and EINSTEIN PE studies. Institutional review board approval was received and written informed consent was obtained from each patient for the original studies and subsequent analyses.

Study Setting and Population

The EINSTEIN DVT and EINSTEIN PE studies were randomized, open-label studies that compared the efficacy and safety of rivaroxaban with standard therapy (enoxaparin/VKA) in patients with acute, symptomatic DVT and/or PE.6,7 Patients were eligible if they were of legal age (i.e., older than 18 years in most countries and older than 21 years in some countries) and had acute, symptomatic, objectively confirmed DVT and/or PE. Briefly, patients were ineligible if they had received therapeutic doses of LMWH, UFH, or fondaparinux for more than 48 hours or if they had received more than a single dose of a VKA before randomization; if thrombectomy had been performed, a vena cava filter placed, or a fibrinolytic agent administered for treatment of the current episode; or if they had any contraindication listed in the local labeling of enoxaparin, warfarin, or acenocoumarol. Exclusion criteria were another indication for a VKA; creatinine clearance (CrCl) < 30 mL/min; clinically significant liver disease; active bleeding or a high risk of bleeding contraindicating anticoagulant treatment; an alanine aminotransferase level that was three times the upper limit of the normal range or higher; systolic blood pressure > 190 mm Hg or diastolic blood pressure > 110 mm Hg; bacterial endocarditis; childbearing potential without proper contraceptive measures, pregnancy, or breastfeeding; concomitant use of a strong inhibitor of cytochrome P450 3A4 or a cytochrome P450 3A4 inducer; or a life expectancy shorter than 3 months.6,7

Study Protocol

Patients assigned to rivaroxaban were given 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily. Patients who were assigned to standard therapy received enoxaparin at a dose of 1.0 mg/kg of body weight twice daily and either warfarin or acenocoumarol, started within 48 hours after randomization. Study
medication was started immediately after randomization. However, for rivaroxaban patients who received parenteral anticoagulation prior to randomization, the first administration of rivaroxaban was given 4, 12, and 24 hours after cessation of intravenous (IV) UFH, LMWH with a twice-daily regimen, and fondaparinux or LMWH with a once-daily regimen, respectively.

Enoxaparin was discontinued when the INR was ≥2.0 for 2 consecutive days and the patient had received ≥5 days of enoxaparin treatment. To avoid overexposure with initial heparins, the EINSTEIN protocol allowed prestudy heparin to be included as part of the initial heparin treatment period (≥5 days) in the enoxaparin/VKA treatment arm. Therefore, there was no difference in total treatment duration with heparins in enoxaparin/VKA patients who did or did not receive prestudy heparin. The dose of VKA was adjusted to maintain an INR between 2.0 and 3.0. The INR was initially determined every 2 to 3 days and when stable, at least once a month. Patients were treated for at least 3 months. The treatment duration (3, 6, or 12 months) was decided by the investigator at randomization based on the risk profile of the patient.

Key Outcome Measures
Patients were followed for the intended treatment period and were assessed at fixed intervals that were identical for both treatment arms, using a checklist to elicit information on symptoms and signs of recurrent VTE, bleeding, and adverse events. Patients were instructed to report to the study center immediately if any of these symptoms or signs occurred. In the case of suspected VTE, objective testing was required. Repeat diagnostic imaging to detect asymptomatic changes in clot size was not performed.

The primary efficacy outcome was acute, symptomatic recurrent VTE, which was defined as a composite of DVT and nonfatal or fatal PE.6,7,14 Death was classified as due to PE, bleeding, or other established diagnoses. PE was considered the cause of death if there was objective documentation of the condition or if death could not be attributed to a documented cause and PE could not be confidently ruled out. The principal safety outcome was clinically relevant bleeding, which was defined as a composite of major and nonmajor clinically relevant bleeding.6,7,14 Bleeding was defined as major if it was clinically overt and associated with a decrease in the hemoglobin level of ≥2.0 g/dL, led to the transfusion of ≥2 units of red blood cells; was intracranial or retroperitoneal or occurred in another critical site; or contributed to death. Nonmajor clinically relevant bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of a study drug, or discomfort or impairment of activities of daily life. All suspected outcome events were classified by a central adjudication committee whose members were unaware of the treatment assignment.

Data Analysis
The statistical software used was SAS versions 9.1 and 9.2. The duration of prestudy treatment with heparins was calculated as the difference between the timing of the first and last dose, plus the duration of pharmacological effect after this last dose. This duration was 4 hours for IV UFH, 12 hours for LMWH with a twice-daily regimen, and 24 hours for fondaparinux and LMWH with a once-daily regimen.

Baseline characteristics were compared between patients who did and did not receive prestudy heparin, using analysis of variance or the van Elteren test, stratified by intended treatment duration, treatment group, and index event and the Cochran-Mantel-Haenszel test, stratified by intended treatment duration, treatment group, and index event, for categorical variables. All efficacy analyses were performed in the intention-to-treat population and concerned events during the first 3 months. The bleeding analyses were performed in the safety population, defined as patients who received at least one dose of study drug, and concerned events during the first 14 days. These analyses were done using a Cox proportional-hazards model, stratified according to the intended duration of treatment and index event (DVT/PE) and adjusted for presence of active cancer at baseline. These analyses were first performed without further adjustment (crude hazard ratio [HR]). Adjusted HRs were then calculated, taking into account factors that were significantly different among the patients who did and did not receive prestudy heparin or that were associated with the primary efficacy or bleeding outcomes, respectively. p-values for interaction in treatment effect between patients who did and did not receive prestudy heparin were calculated for adjusted HRs only. Kaplan-Meier curves were generated to display the distribution of events over time.

RESULTS
Patient Characteristics and Heparin Use
A total of 8,821 patients were randomized. Of these, 6,937 (83.8%) patients received prestudy heparin and 1,344 (16.2%) patients did not receive prestudy heparin. Most patients (4,840 of 6,937, 69.8%) received prestudy heparin for 1 day or less. A total of 1,986 (28.6%) patients received prestudy heparin for longer than 1 to 2 days, and only 111 (1.6%) patients received prestudy heparin for more than 2 days. The mean (±SD) duration

| Table 1 Duration of Prestudy Heparin Use |
|----------------------------------------|
| Variable | Rivaroxaban (n = 4,150) | Enoxaparin/VKA (n = 4,131) |
| Presudy heparin use (days), n (%) | | |
| ≤0.5 | 337 (8.1) | 378 (9.2) |
| 1 | 2,103 (50.7) | 2,022 (48.9) |
| >1–2 | 1,006 (24.2) | 980 (23.7) |
| >2 | 55 (1.3) | 56 (1.4) |
| Mean (±SD)* | 1.04 (±0.74) | 1.03 (±0.42) |
| Median (IQR)* | 1.00 (0.79 to 1.11) | 1.00 (0.78 to 1.10) |

*pPatients who received prestudy heparin only.

IQR = interquartile range; VKA = vitamin K antagonist
for prestudy heparin treatment was 1.04 (±0.74) days in the rivaroxaban treatment group and 1.03 (±0.42) days in the standard treatment group (Table 1). In the enoxaparin/VKA group, the median duration of heparin treatment was 7.5 days (interquartile range [IQR] = 5.9 to 10.1 days) in patients who received prestudy heparin and 7.1 days (IQR = 5.2 to 10.1 days) in those who did not.

Patient demographics, including age, sex, and CrCl, were similar among patients who did or did not receive prestudy heparin, although mean body mass index was significantly lower in patients who did not receive prestudy heparin (Table 2). Other factors that might influence clinical outcomes, such as the index event (spontaneous or secondary), or previous episodes of DVT/PE prior to randomization, were similar between groups (Table 2). In all subgroups of patients, except those from Asia, the majority received prestudy heparin; however, its use was less frequent in patients with DVT only, those with limited severity of VTE, and those with cancer (Table 2).

Recurrent VTE
Of the 1,344 patients who did not receive prestudy heparin, 28 (2.1%) patients developed recurrent VTE during the first 3 months (Table 3). The incidence of the primary efficacy outcome was similar in patients receiving rivaroxaban (15 of 649, 2.3%) and enoxaparin/VKA (13 of 695, 1.9%), corresponding to a crude HR of 1.22 (95% confidence interval [CI] = 0.58 to 2.57) and an adjusted HR of 1.11 (95% CI = 0.52 to 2.37; adjusted for age, presence of active cancer at baseline, CrCl, severity of index event categories, and geographic regions). Of the 6,937 patients who received prestudy heparin, 123 (1.8%) developed recurrent VTE. These incidences were similar in patients receiving rivaroxaban (54 of 3,501, 1.5%) and enoxaparin/VKA (69 of 3,436, 2.0%), corresponding to a crude HR of 0.75 (95% CI = 0.53 to 1.07) and an adjusted HR of 0.74 (95% CI = 0.52 to 1.06; \( p_{\text{interaction}} = 0.32 \)). There was no relationship between the duration of prestudy heparin treatment and the incidence of recurrent VTE (\( p_{\text{trend}} = 0.77 \), Table 3). The distribution of events over time is shown in Figure 1.
Bleeding
Of the 1,344 patients who did not and the 6,937 patients who did receive prestudy heparin, 1,333 and 6,913 patients, respectively, received at least one dose of study drug. Of the 1,333 patients who did not receive prestudy heparin, 54 (4.1%) developed major or nonmajor clinically relevant bleeding events during the first 14 days. The incidences were similar in patients receiving rivaroxaban (24 of 645, 3.7%) and enoxaparin/VKA (30 of 688, 4.4%), corresponding to a crude HR of 0.84 (95% CI = 0.49 to 1.44) and an adjusted HR of 0.81 (95% CI = 0.46 to 1.40). Of the 6,913 patients who received prestudy heparin, 209 (3.0%) developed major or nonmajor clinically relevant bleeding events. The incidences were similar in patients receiving rivaroxaban (105 of 3,485, 3.0%) and enoxaparin/VKA (104 of 3,428, 3.0%), corresponding to a crude HR of 0.99 (95% CI = 0.75 to 1.30) and an adjusted HR of 0.98 (95% CI = 0.75 to 1.29; pinteraction = 0.68).

Of the 1,333 patients who did not receive prestudy heparin, nine (0.7%) patients developed major bleeding during the first 14 days. The incidence was numerically lower, but not significantly lower, in patients receiving rivaroxaban (two of 645, 0.3%) and those receiving enoxaparin/VKA (seven of 688, 1.0%), with a crude HR of 0.28 (95% CI = 0.06 to 1.35) and an adjusted HR of 0.33 (95% CI = 0.07 to 1.68; adjusted for age, presence of active cancer at baseline, CrCl, weight, severity of index event categories, and geographic region). Of the 6,913 patients who received prestudy heparin, 31 (0.4%) patients had major bleeding events. The incidence of this outcome was also numerically lower in patients receiving rivaroxaban (11 of 3,485, 0.3%) and those receiving enoxaparin/VKA (20 of 3,428, 0.6%), with a crude HR of 0.52 (95% CI = 0.25 to 1.1) and an adjusted HR of 0.49 (95% CI = 0.23 to 1.03; pinteraction = 0.62).

DISCUSSION
This post hoc analysis of data from the EINSTEIN program showed that LMWH, UFH, or fondaparinux was used prior to randomization in the majority of patients in the EINSTEIN studies. The duration of prestudy heparin treatment was limited to 1 day or less in most patients, and compared with those who did not receive prestudy heparin, no difference was observed in the incidences of recurrent VTE or bleeding in patients receiving monotherapy with rivaroxaban.

Although patients in the EINSTEIN DVT and EINSTEIN PE studies were followed for clinical outcomes for up to 12 months, we elected to limit the time window for this analysis to 3 months for recurrent VTE and 14 days for bleeding. This decision was based on previous studies that observed an excess of recurrent venous thromboembolic events during a period of 3 months in patients with DVT who received either inadequate doses of initial heparin, or no initial heparin at all,10–12 and the short-term effects of heparins on the occurrence of bleeding. Limiting the time window for bleeding to the actual duration of enoxaparin plus 2 days was not possible because patients receiving rivaroxaban did not receive placebo/enoxaparin. Hence, a 14-day window seemed most appropriate, particularly because the median duration of heparin use and the IQRs were almost identical in the prestudy heparin and no prestudy heparin groups.

The relative efficacy and safety of rivaroxaban versus enoxaparin/VKA did not differ in patients who did or did not receive prestudy heparin, and the observed incidences of recurrent VTE, nonmajor clinically relevant bleeding, and major bleeding were all similarly low.

**Table 3**

Recurrent Venous Thromboembolism up to 3 Months in Relation to Duration of Prestudy Heparin Use

| Variable | Rivaroxaban | Enoxaparin/VKA |
|----------|-------------|----------------|
| No prestudy heparin use, n/N (%) | 15/649 (2.3) | 13/695 (1.9) |
| Prestudy heparin use (days), n/N (%) | 54/3,501 (1.5) | 69/3,436 (2.0) |
| ≤0.5 | 8/337 (2.4) | 9/379 (2.4) |
| 1 | 31/2,103 (1.5) | 36/2,022 (1.8) |
| >1–2 | 15/1,006 (1.5) | 23/980 (2.3) |
| >2 | 0/55 (0.0) | 1/56 (1.8) |

VKA = vitamin K antagonist.
This implies that in patients with DVT or PE, an initial course of heparin is not required before rivaroxaban is started. The results also indicate that it is feasible to start rivaroxaban even in patients who have already been given a few doses of LMWH. Observations from this study support a shift in the care of patients with VTE. The availability of oral drugs that do not require prior parenteral drug administration is expected to increase the number of patients who can be treated directly at home, including low-risk patients with acute PE. This potential shift in care is supported by evidence from EINSTEIN DVT and EINSTEIN PE, in which hospitalized patients receiving rivaroxaban had a significantly shorter length of stay compared with patients receiving enoxaparin/VKA. Therefore, use of oral rivaroxaban could reduce the costs and inconvenience of hospital admission and obviate the need for instructing patients on the technique for administering subcutaneous injections. In addition, the risk of heparin-induced thrombocytopenia, which is still reported in patients receiving LMWH, could be minimized.

LIMITATIONS

The methodological strengths and limitations of the EINSTEIN DVT and EINSTEIN PE studies have been discussed previously. For the current analysis, there are additional aspects that require comment. The EINSTEIN DVT and EINSTEIN PE protocols allowed for the use of heparins with a prerandomization time window of less than 48 hours, to bridge the period needed to finalize the diagnostic workup and study requirements. It should be noted that a direct comparison of study outcomes in patients who did or did not receive prestudy heparin is flawed, even if adjusted for important differences at baseline. The reason for this is that it is likely that intended randomization into the study was canceled in patients who developed recurrent VTE or bleeding during the use of prestudy heparin. By contrast, patients who had uneventful courses during the prestudy period would have been randomized. This selective inclusion, for which no adjustment can be made, may have downwardly affected the rate of study outcomes in patients who received prestudy heparin. Conversely, the head-to-head comparison of rivaroxaban and enoxaparin/VKA within the subgroups, defined by the use or nonuse of prestudy heparin, is still valid, even if the comparison of the observed HRs within these subgroups needs adjustment for baseline differences. Patients who received prestudy heparin were more likely to have PE and less likely to have DVT compared with those who did not receive heparin. These patients were also more likely to have VTE of intermediate severity and less likely to have VTE of limited or extensive severity, less likely to have active cancer, and less likely to be from Asia. The majority of patients who did not receive prestudy heparin were randomized immediately after admission to the hospital. Therefore, the analysis was adjusted for these clinically important variables, and the p-values for interactions were calculated for the adjusted HRs only.

CONCLUSIONS

Most patients participating in the EINSTEIN DVT and EINSTEIN PE studies received one or two doses of heparin prior to randomization. No notable differences were found regarding the incidence of subsequent recurrent VTE or bleeding in patients treated with rivaroxaban who did or did not receive prestudy heparin, compared with enoxaparin/VKA recipients.

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