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Full Length Article

Impact of age, comorbidity, and polypharmacy on the efficacy and safety of edoxaban for the treatment of venous thromboembolism: An analysis of the randomized, double-blind Hokusai-VTE trial

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ABSTRACT

Background: Many patients with venous thromboembolism (VTE) are elderly, have multiple comorbidities and take several concomitant medications. Physicians may prefer warfarin over direct oral anticoagulants (DOACs) in such patients because comparative data are lacking. This analysis was designed to determine the effects of advanced age, comorbidities, and polypharmacy on the efficacy and safety of edoxaban and warfarin in patients with VTE.

Methods: Using data from the Hokusai-VTE study, we report rates of recurrent VTE and of clinically relevant bleeding by age category (< 65, 65–75, and ≥ 75; < 80 versus ≥ 80 years), and by number of comorbidities (0, 1–2, > 2) and concomitant medications (< 3, 3–5, > 5). Hazard ratios (HR) and corresponding 95% confidence intervals (CI) for edoxaban versus warfarin were determined and Kaplan-Meier methodology was used to construct time-to-event curves. At 3 months, pre- and postdose levels of edoxaban were measured using mass spectrometry. For warfarin-treated patients, the time in therapeutic range was calculated. The study was approved by institutional review boards; informed consent was obtained.

Results: Recurrent VTE increased with advanced age, multiple comorbidities, and polypharmacy in warfarin-treated patients but not with edoxaban. Edoxaban was more effective than warfarin in patients ≥ 75 years of age and in those with multiple comorbidities. In the 517 patients over 80 years of age, recurrent VTE occurred in 2.8% given edoxaban and in 5.7% given warfarin (HR 0.51, 95% CI 0.21–1.24). Bleeding increased with age, comorbidity, and polypharmacy regardless of treatment, but the relative safety of edoxaban versus well-managed warfarin was maintained. Age, comorbidity, and polypharmacy did not impact edoxaban concentrations.

Conclusions: These data suggest that a once-daily fixed dose of edoxaban is more effective and at least as safe as warfarin in high-risk VTE patients identified by older age, more comorbidities, and polypharmacy.

Clinical trial registration: NCT00986154

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1. Introduction

Guidelines suggest direct oral anticoagulants (DOACs) as the preferred treatment for venous thromboembolism (VTE) [1]. DOACs offer similar efficacy and improved safety compared with warfarin while simplifying VTE treatment by using fixed dosing without routine coagulation monitoring. However, many physicians are reluctant to prescribe DOACs in patients with advanced age, multiple comorbidities, or taking numerous medications, and often prefer monitored warfarin [2].

Although studies have reported on the efficacy and safety of DOACs for the treatment of VTE in the elderly, there are limited data on polypharmacy and comorbidities, or outcomes were described separately in the very elderly. The lack of such data may explain the underuse of DOACs for these complex patients who are known to be at increased risk for both VTE recurrence and anticoagulation-related bleeding.

The Hokusai-VTE trial demonstrated that once-daily edoxaban was as effective as well-managed warfarin for preventing recurrent VTE and was associated with significantly less bleeding [3]. The objective of this analysis was to compare the effects of advanced age, comorbidities, and polypharmacy on the efficacy and safety of edoxaban and warfarin in this study.

2. Methods

2.1. Study design and oversight

Hokusai-VTE was a randomized, double-blind trial that compared edoxaban with warfarin after an initial course of heparin in patients with acute symptomatic VTE. We have previously reported the study design and results. (ClinicalTrials.gov identifier: NCT00986154) [3,4]. All suspected outcomes were adjudicated by an independent committee unaware of study group assignment. The Hokusai-VTE protocol was reviewed by the institutional review board at each institution and all patients provided written informed consent.

In brief, patients enrolled in Hokusai-VTE were 18 years of age and older without an upper age limit, and had confirmed acute, symptomatic proximal deep-vein thrombosis (DVT) or acute, symptomatic pulmonary embolism (PE). Relevant exclusion criteria included a creatinine clearance < 30 mL/min, and use of chronic dual antiplatelet therapy, aspirin in doses above 100 mg per day, non-steroidal anti-inflammatory drugs, or potent P-glycoprotein (P-gp) inhibitors (such as HIV protease inhibitors and systemic azole antifungals) [3].

2.2. Study treatment

All patients received open-label unfractionated heparin or low-molecular weight-heparin for at least 5 days. Edoxaban or warfarin was administered in a double-blind double-dummy fashion for at least 3 months and up to 12 months. Duration of treatment was at the discretion of the investigator and was based on evaluation of the relative benefits and risks of continuing anticoagulation at 3 and 6 months.

Edoxaban was given as a dose of 60 mg once daily. The dose was reduced to 30 mg once daily in patients with a creatinine clearance of 30 to 50 mL/min, a body weight of 60 kg or less, or taking concomitant verapamil or quinidine. The warfarin dose was adjusted to maintain an international normalized ratio (INR) between 2.0 and 3.0 [4]. To maintain blinding, sham INR measurements were provided for patients randomized to edoxaban [3].

2.3. Pharmacokinetic and pharmacodynamic assessments

Blood samples were taken pre- and post-edoxaban dosing at steady state (the month 3 visit) for determination of edoxaban levels. Edoxaban levels were quantified using liquid chromatography-tandem mass spectrometry (Advion Bioservices, Ithaca, New York). For warfarin-treated patients, the time in therapeutic range (TTR) was calculated as previously described [5].

2.4. Outcome measures

All patients, regardless of treatment duration, were followed for 12 months or until the end-of-study date. The primary efficacy outcome was the incidence of symptomatic recurrent VTE (defined as DVT and/or fatal or nonfatal PE) during the overall study period. The principal safety outcome was the incidence of clinically relevant bleeding (the composite of major and clinically relevant nonmajor bleeding). Major bleeding was defined as overt bleeding that was associated with a reduction in hemoglobin of ≥ 2 g/dL or requiring transfusion of 2 or more units of blood, occurred at a critical site, or contributed to death. Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but required medical intervention, unscheduled contact with a clinician, interruption of study drug, or discomfort or impairment of daily activities. The prespecified net clinical outcome was defined as the composite of first on-treatment recurrent VTE or first major bleed [3,4].

2.5. Statistical analyses

Analyses were performed using the previously reported methodology [3,4]. Patients were categorized by age (< 65, 65–75, and ≥ 75 years; as well as below and above 80 years). The number of medications at baseline was collected, and patients were divided into 3 categories defined by these numbers. Based on tertiles, cutoffs of 0 to 2, 3 to 5, and 6 or more medications were selected. To categorize patients by concomitant medical conditions, patients were divided based on a number of a priori selected conditions that were collected at baseline. These included known history of hypertension, diabetes, dyslipidemia, cardiovascular disease, valvular heart disease, heart rhythm disorder, cerebrovascular disease, renal disease, hepatic disease, pulmonary disease, rheumatoid arthritis, cancer, osteoporosis, and fracture; alcohol use; smoking; any other significant medical or surgical history within the past 10 years; or history of life-threatening bleeding, active bleeding or at high risk for bleeding. We compared patients without any concomitant medical conditions with those with 1 or 2, and 3 or more medical conditions. In a sensitivity analysis, we reported outcome events in the subgroup of elderly patients (age ≥ 65 years) who also had > 2 concomitant medical conditions or > 5 concomitant medications.

The frequency of baseline characteristics was calculated separately for each category. Efficacy analyses were conducted in the modified intent-to-treat population (mITT), which included all randomized patients who received at least 1 dose of study drug. The primary analysis consisted of all efficacy outcomes occurring from randomization through 12 months or study closure (overall study period). The primary efficacy outcome was also assessed for the on-treatment period (the time during which patients received study drug or within 3 days after discontinuation or interruption of study drug). Analysis of bleeding outcomes also included patients who received at least 1 dose of study medication, and was conducted for the on-treatment period. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) for edoxaban versus warfarin were determined.

A Cox proportional hazards model that included treatment, index event (DVT or PE), and presence of a risk factor as covariates was used to evaluate the time to the first primary efficacy outcome and the time to the first safety outcome. The assumption of proportional hazards of recurrent VTE was investigated graphically (e.g., log(-log)-plots). The plot showed reasonable fit to the proportional hazards assumption. Kaplan-Meier methodology was used to construct time-to-event curves.

The pre- and postdose edoxaban levels are presented in box-and-whisker-plots, which indicate the medians, the interquartile ranges (IQR), and the 10th and 90th percentiles of drug levels.