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The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

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Objectives The goal of this study was to analyze the impact of dabigatran plasma concentrations, patient demographics, and aspirin (ASA) use on frequencies of ischemic strokes/systemic emboli and major bleeds in atrial fibrillation patients.

Background The efficacy and safety of dabigatran etexilate were demonstrated in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, but a therapeutic concentration range has not been defined.

Methods In a pre-specified analysis of RE-LY, plasma concentrations of dabigatran were determined in patients treated with dabigatran etexilate 110 mg twice daily (bid) or 150 mg bid and correlated with the clinical outcomes of ischemic stroke/systemic embolism and major bleeding using univariate and multivariate logistic regression and Cox regression models. Patient demographics and ASA use were assessed descriptively and as covariates.

Results Plasma concentrations were obtained from 9,183 patients, with 112 ischemic strokes/systemic emboli (1.3%) and 323 major bleeds (3.8%) recorded. Dabigatran levels were dependent on renal function, age, weight, and female sex, but not ethnicity, geographic region, ASA use, or clopidogrel use. A multiple logistic regression model (c-statistic 0.657, 95% confidence interval [CI]: 0.61 to 0.71) showed that the risk of ischemic events was inversely related to trough dabigatran concentrations ($p = 0.045$), with age and previous stroke (both $p < 0.0001$) as significant covariates. Multiple logistic regression (c-statistic 0.715, 95% CI: 0.69 to 0.74) showed major bleeding risk increased with dabigatran exposure ($p < 0.0001$), age ($p < 0.0001$), ASA use ($p < 0.0003$), and diabetes ($p = 0.018$) as significant covariates.

Conclusions Ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations. Age was the most important covariate. Individual benefit–risk might be improved by tailoring dabigatran dose after considering selected patient characteristics. (Randomized Evaluation of Long Term Anticoagulant Therapy [RE-LY] With Dabigatran Etexilate; NCT00262600) (J Am Coll Cardiol 2014;63:321–8) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AF = atrial fibrillation
ASA = aspirin
bid = twice daily
CAD = coronary artery disease
CI = confidence interval
CrCl = creatinine clearance
DE = dabigatran etexilate
DE 110 = dabigatran etexilate 110 mg twice daily
DE 150 = dabigatran etexilate 150 mg twice daily
PK = pharmacokinetic(s)
SEE = systemic embolic event(s)

Dabigatran etexilate (DE), a new, oral, direct thrombin inhibitor was shown in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial to be as effective (110 mg twice daily [bid], DE 110) or more effective (150 mg bid, DE 150) than warfarin, when given as a fixed dose without laboratory monitoring for prevention of stroke and systemic embolism in atrial fibrillation (AF) patients (1–3). The low dose of DE was associated with significantly less bleeding than both warfarin and the high dose of DE. Compared with DE 110, exposure to dabigatran was increased by 36% with DE 150 (4), resulting in a 39% reduction in strokes/systemic emboli but at the cost of a 16% increase in major bleeding (1,2). Thus, the RE-LY trial established dose–response relationships for stroke prevention and bleeding with DE. However, there is large variability in the plasma concentrations achieved with any given dose, depending on absorption, renal function, and other patient factors (4–6). DE is a prodrug metabolized in the plasma and liver to the active moiety dabigatran (6). How much the risk of stroke or bleeding also varies across the concentration range has important implications for the benefit–risk ratio and the possibility to tailor the dose in individual patients. Currently, it is unknown whether there is a single concentration range where the balance between thromboembolic events and bleeding events is optimal for all AF patients.

The rates of stroke and major bleeding in DE-treated patients have been investigated across a variety of patient subgroups (1,7), but correlations of stroke and bleeding risk with individual plasma concentrations have not been presented. The aims of this pharmacokinetic (PK) analysis of the RE-LY trial were to explore the association between plasma concentrations and efficacy and safety outcomes, and to identify factors affecting the variability of plasma concentrations of dabigatran and their impact on outcome events in AF patients with an indication for oral anticoagulation.

Methods

The design and results of the RE-LY study have been previously published (1–3). Briefly, the primary objective of RE-LY was to establish the noninferiority of 2 doses of DE compared with warfarin for stroke prevention in patients with AF and 1 additional risk factor for stroke. This trial randomized 18,113 AF patients to 1 of 2 blinded doses of DE, DE 110 or DE 150, or to dose-adjusted warfarin titrated to an international normalized ratio of 2 to 3. Median follow-up was 2.0 years. The study, including the PK sampling, was approved by all appropriate national regulatory authorities and ethics committees. All patients provided written informed consent before study entry.

All patients with a valid blood sample and all ischemic stroke/systemic embolic events (SEE) or bleeding events that occurred on-treatment in these patients were included in the analysis, regardless of when the event occurred in relation to the sampling. Patients who were off-treatment at the time of sampling or the time of event were not included in the analysis. All primary and secondary outcome events were blindly and doubly adjudicated. The primary RE-LY study outcome was stroke or systemic embolism. Stroke type was subdivided into ischemic, hemorrhagic, and unknown. Definitions of RE-LY endpoints are described elsewhere (1,3). $CHADS_2$ score is a simple validated risk score that assigns 1 point for a history of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and 2 points for a history of stroke or transient ischemic attack. CHA_2DS_2-VASc (8) and HAS-BLED (9) are other methods to assess risk for stroke or bleeding in AF patients.

PK and statistical methods. Peak and trough samples at steady state were collected for determination of drug concentration, activated partial thromboplastin time, and ecarin clotting time at 1-month post-randomization in all DE subjects who gave consent to participate, regardless of the time of any ischemic or bleeding event that occurred. Samples were collected from patients in all geographic regions. The frequencies generally approximated the number of recruited subjects. For trough concentrations, only samples collected within 10 to 16 h after the previous DE dose were considered. Similarly, for post-dose samples, only samples collected within 1 to 3 h after dosing were considered. Approximately 12% of samples were excluded from evaluation because of questionable records in blood sampling date/time or in administration date/time. Additional samples were taken at 3, 6, and 12 months from 2,143 subjects who participated in a PK substudy. For analyses reported here, the data were merged with the data from the substudy and analyzed together. The first trough and post-dose samples fulfilling the time-window rule were used from these subjects with multiple blood samples. The population PK (4) and pharmacodynamic data (activated partial thromboplastin time and ecarin clotting time) will be reported elsewhere.

Plasma concentrations of nonconjugated (free) dabigatran and of total dabigatran after alkaline cleavage of conjugates were determined by a validated high-performance liquid chromatography tandem mass spectrometry method at AAIPharma Deutschland GmbH & Co. KG, Neu-Ulm, Germany (10). Total dabigatran concentration was determined in all PK plasma samples, whereas nonconjugated dabigatran was determined in a subset ($n = 1,085$) of samples in order to assess the prevalence of dabigatran acylglucuronides in this population.

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