Stroke

BRIEF REPORT

Clinical Outcomes of Anticoagulated Patients With Atrial Fibrillation After Falls or Head Injury: Insights From RE-LY

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BACKGROUND: Falls are always a concern regarding the balance of risk/benefit in patients with atrial fibrillation treated with anticoagulants. In this analysis, we aimed to evaluate the outcomes of patients that had a fall/head injury reported in the RE-LY clinical trial (Randomized Evaluation of Long-Term Anticoagulation Therapy) and to explore the safety of dabigatran (a nonvitamin K antagonist oral anticoagulant).

METHODS: We performed a post hoc retrospective analysis of intracranial hemorrhage and major bleeding outcomes in the RE-LY trial with 18 113 individuals with atrial fibrillation, according to the status occurrence of falls (or head injury) reported as adverse events. Multivariate Cox regression models were used to provide adjusted hazard ratio (HR) and 95% CI.

RESULTS: In the study, 974 falls or head injury events were reported among 716 patients (4%). These patients were older and had more frequently comorbidities such as diabetes, previous stroke, or coronary artery disease. Patients with fall had a higher risk of major bleeding (HR, 2.41 [95% CI, 1.90–3.05]), intracranial hemorrhage (HR, 1.69 [95% CI, 1.35–2.13]), and mortality (HR, 3.91 [95% CI, 2.51–6.10]) compared to those who did not have reported falls or head injury. Among patients who had falls, those allocated to dabigatran showed a lower intracranial hemorrhage risk (HR, 0.42 [95% CI, 0.18–0.98]) compared with warfarin.

CONCLUSIONS: In this population, the risk of falls is important and confers a worse prognosis, increasing intracranial hemorrhage, and major bleeding. Patients who fell and were under dabigatran was associated with lower intracranial hemorrhage risk than those anticoagulated with warfarin, but the analysis was merely exploratory.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: anticoagulation ■ falls ■ frailty ■ intracranial hemorrhages ■ warfarin

Atrial fibrillation is the most prevalent persistent arrhythmia, and it is estimated to be present in about 33 million individuals worldwide.[1] Thrombus or thrombi formation due to incompetent atrial contraction may result in embolism to cerebral arteries leading to stroke, which is the main consequence of atrial fibrillation.[2,3] Anticoagulants are therefore essential to prevent thrombus formation and embolic stroke in patients with atrial fibrillation.[4,5]

These drugs increase the risk of bleeding, and such risk is used as an argument against its introduction in more frail patients.[6] To overcome these hypothetical barriers, some studies using vitamin K antagonists claimed that it would be needed 295 falls to have 1 episode of intracranial hemorrhage (ICH).[7] The direct oral anticoagulants or nonvitamin K antagonists oral anticoagulants showed at least noninferiority regarding the risk of stroke or systemic embolism compared with vitamin

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Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
HR	hazard ratio
ICH	intracranial hemorrhage
RE-LY	The Randomized Evaluation of Long-Term Anticoagulation Therapy
STROBE	Strengthening the Reporting of Observational studies in Epidemiology

K antagonists.[8] The lack of important interactions with other drugs or food and the fact that it is needless to monitor international normalized ratio as opposed to vitamin K antagonists, warranting for non-vitamin K antagonists oral anticoagulants some practical advantages and improved patients' satisfaction.[9] The non-vitamin K antagonists oral anticoagulants also showed an improved safety profile, especially regarding the risk of major bleeding and ICH.[10,11]

In this study, we aimed to evaluate the frequency of falls among patients with atrial fibrillation enrolled in The RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). We also intended to assess the outcomes of patients with atrial fibrillation that had a fall or head injury, and to explore whether dabigatran treatment interacts with the outcomes in this specific population.

METHODS

This was a post hoc analysis of the RE-LY trial that followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.[12] RE-LY was a randomized trial designed to compare 2 fixed doses of dabigatran, each administered in a blinded manner, with open-label use of warfarin in patients who had atrial fibrillation and were at increased risk for stroke.[13] It enrolled a total of 18 113 patients who were assigned to either one of 2 doses of dabigatran (110 or 150 mg) twice daily or an international normalized ratio-adjusted dose of warfarin. RE-LY trial was an open-label noninferiority trial that evaluated the impact of interventions in stroke or systemic embolism.[13] The patients were followed for a median period of 2.0 years.

In this study, it was our objective to estimate the frequency of fall or head injuries, reported by investigators as adverse events, among patients treated with oral anticoagulation in the RE-LY trial (Figure S1). Written informed consent for trial participation was provided by each patient or their legally authorized representative. Institutional review board approval was obtained at each enrolling site/country of the RE-LY trial. As this study only used deidentified, no further IRB approval was required. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Boehringer Ingelheim via the repository Vivli.[14]

Baseline data regarding clinical and demographic characteristics of patients that had falls/head injury were presented as proportion or means and compared with patients without this adverse event. Between-group comparisons were performed through χ^2 tests or *T* tests (according with the type of variable). Time-to-event analyses were performed using Cox proportional hazards models, and hazard ratio (HR) with 95% CI were reported for single variable models (falls/head injury) and adjusted hazard ratio (aHR) for age, sex, body mass index, creatinine clearance, previous history of myocardial infarction, stroke, or heart failure and comorbidities as hypertension, diabetes, as well as the use of drugs and when adequate the randomization to dabigatran or vitamin K antagonists (Table S1).

Within the subgroup of patients who had falls, we also performed an exploratory analysis evaluating the risk of major bleeding, ICH, and all-cause mortality in patients allocated to dabigatran versus warfarin.

Statistical analyses were performed using Stata/SE software 17.0 (StataCorp). Two-sided *P* values <0.05 were considered statistically significant.

RESULTS

From the 18 113 patients in RE-LY, we identified 716 fallers, some of which with multiple falls, accounting for a total of 974 falls (Figure S1). Among patients with falls 24% had 2 or more falls and (169 patients) and 8% had 3 or more falls reported (57 patients; Table S2). Individual characteristics of these 2 subpopulations—fallers and nonfallers and their differences are depicted in Table 1.

When comparing both groups in terms of safety outcomes, there was a statistically significant higher rate of mortality in those patients who had falls/head injury (10.5% versus 7.4%; P=0.003) as well a higher prevalence of ICH (0.7% versus 3.8%; P<0.001; Figure S2) and major bleeding (6.2% versus 15.2%; P<0.001).

On multivariate analysis using Cox method, falling was an independent risk factor for ICH (aHR, 5.07 [95% CI, 3.27–7.80]), major bleeding (aHR, 2.11 [95% CI, 1.68–2.64]), and mortality (aHR, 2.71 [95% CI, 2.15–3.43]; Table 2).

While the anticoagulation treatment allocation showed to have significant interaction with the incidence of falls ($P_{interaction}$=0.02) with lower falls in the dabigatran arms (Table 1), there were also differences regarding safety outcomes, in respect to the allocated anticoagulation treatment (Table S3). Patients with dabigatran had a lower risk of ICH when compared with those treated with warfarin, after adjusting for potential confounders (Tables S4 and S5): Dabigatran aHR, 0.41 [95% CI, 0.18–0.95]; dabigatran 110 mg aHR, 0.59 [95% CI, 0.23–1.49]; dabigatran 150 mg aHR, 0.24 [95% CI, 0.07–0.86]; Table S2. Notwithstanding these data, the estimates of Dabigatran versus Warfarin on major bleeding events in this subgroup were not statistically significant (Dabigatran aHR, 0.81 [95% CI, 0.52–1.26]; dabigatran 110 mg aHR, 0.77 [95% CI, 0.45–1.33]; Dabigatran 150 mg aHR, 0.77 [95% CI, 0.45–1.33]).

Table 1. Main Characteristics of the Group of Patients Who Had Falls and Those Who Did Not Fall

Characteristics	Fallers (n=716)	Nonfallers (n=17397)	*P* value
Age	75.64±7.32	71.22±8.60	*P*<0.001
Age>75	439 (61)	6803 (39)	*P*<0.001
Female	315 (44)	6283 (36)	*P*<0.001
BMI	28.23±5.66	28.77±5.80	*P*=0.015
Creatinine clearance	64.77±24.05	73.24±27.87	*P*<0.001
Myocardial infarction	134 (19)	2871 (17)	*P*=0.12
Stroke	182 (25)	3771 (21)	*P*=0.018
Heart failure	213 (30)	5580 (32)	*P*=0.19
Diabetes	192 (27)	4029 (23)	*P*=0.023
CAD	249 (35)	4785 (28)	*P*<0.001
Hypertension	557 (78)	13726 (79)	*P*=0.48
ACE inhibitors	303 (42)	7820 (45)	*P*=0.17
ARBs	177 (25)	4159 (24)	*P*=0.62
Aspirin	292 (41)	6861 (39)	*P*=0.47
Amlodipine	85 (12)	1891 (11)	*P*=0.40
Beta-blocker	449 (63)	10949 (63)	*P*=0.90
Digoxin	182 (25)	5108 (29)	*P*=0.023
Diltiazem	90 (13)	1594 (9)	*P*=0.002
Diuretic	396 (55)	8842 (51)	*P*=0.019
H2 Blocker	51 (7)	707 (4)	*P*<0.001
PPI	144 (20)	2423 (14)	*P*<0.001
Statin	363 (51)	7694 (44)	*P*<0.001
Verapamil	40 (6)	1031 (6)	*P*=0.71
Paroxysmal atrial fibrillation	272 (38)	5671 (33)	*P*=0.003
Dabigatran 110 mg	232 (32)	5783 (33)	*P*=0.64
Dabigatran 150 mg	214 (30)	5862 (34)	*P*=0.03
Dabigatran both doses	446 (62)	11645 (67)	*P*=0.01
Warfarin	270 (38)	5752 (33)	*P*=0.01

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BMI, body mass index; CAD, coronary artery disease; H2, histamin-2 receptor; and PPI, proton pump inhibitor.

DISCUSSION

Safety and efficacy of novel anticoagulants have been a topic of discussion for the last decade, with several important randomized controlled trial showing a favorable profile in preventing arterial and venous embolism when comparing to vitamin K antagonists. Data regarding safety in patients who had falls is still required to understand the unmet needs and doubts about the management of anticoagulation in this population. One of the main findings was that about 4% of patients with atrial fibrillation had at least 1 episode of fall or head injury reported in the trial. The proportion of these patients who died was 10.5%, 15% had major bleeding, and 4% had ICH.

Falling was an independent risk factor for mortality, ICH, and major bleeding. Those who fell were older, predominantly female, had a lower body mass index, which is possibly associated with sarcopenia, less muscular strength, balance, and frailty. They had also a higher burden of comorbidities as 1 might have expected, namely chronic kidney disease, previous stroke, diabetes, and coronary artery disease, which further diminishes physical capacity. However, falling remained an independent risk factor for mortality and major hemorrhage even after adjusting for these factors.

ICH is one of the most feared complications, with severe potential neurological implications. Given the fact that most patients anticoagulated are elderly and have major risk factors for falls, safety in this area is fundamental for the success of the therapeutics and its adhesion.

Beyond the evaluation mortality and major hemorrhage associated with falls, this post hoc analysis of RE-LY trial also aimed to explore the safety of dabigatran in this setting.

Among patients with reported falls or head injuries, there was a protective signal of dabigatran safety regarding ICH risk when comparing to patients with warfarin. Despite a trend toward a protective effect in major bleeding after falling with dabigatran, such association met no statistical significance. A possible hypothesis relies on a blunt in the bleeding risk reduction by the gastrointestinal hemorrhage risk, which was increased in dabigatran group in the main analysis of RE-LY, especially with the 150 mg dose.[13]

It is worth noting that the absolute ICH incidence occurred approximately in 1 for each 20 fallers/head injury. This number if by far lower than those claimed by previous data,[7] but our analysis has for sure selective reporting/severity bias, which means that probably the investigators only reported the most severe falls/head injuries (reported by patients or leading for medical services need). This means that the number of patients "required" for the occurrence of ICH is probably higher, acknowledging also that 1 quarter had 2 or more reported falls. The inclusion of head injury also leads to a probable overestimation for the pure fall risk. Nevertheless, we think that these data are informative for healthcare professionals and patients.

Table 2. Outcomes in Patients Who Had Falls Compared With Those Who Did Not Fall

Outcomes	Fallers (n=716)	Nonfallers (n=17397)	*P* value	HR (95% CI) fallers vs non-fallers
Mortality, %	75 (10.50)	1296 (7.4)	*P*=0.003	3.91 (2.51–6.10)
ICH, %	27 (3.8)	130 (0.7)	*P*<0.001	1.69 (1.35–2.13)
Major bleeding, %	109 (15.2)	1073 (6.2)	*P*<0.001	2.41 (1.90–3.05)

HR indicates hazard ratio; and ICH, intracranial hemorrhage.

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It is important to stress that among the risk of bias inherent to this post hoc analysis, it was not possible to retrieve the cause of the fall and the persistence/discontinuation of oral anticoagulation was not ascertained. Due to the advantages of non-vitamin K antagonists oral anticoagulants compared with warfarin in patients candidates to both drugs, it is not expected that robust randomized controlled trials can be conducted to answer this question.

CONCLUSIONS

In this population, the risk of falls is important and confers a worse prognosis, increasing ICH and major bleeding. Patients who fell and were under dabigatran might had lower ICH risk than those anticoagulated with warfarin, but the analysis was merely exploratory.

ARTICLE INFORMATION

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Supplemental Material

Figures S1–S2
Tables S1–S5

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