Safety of High-Dose Dabigatran in Elderly and Younger Patients with a Low Bleeding Risk: A Prospective Observational Study

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Keywords

Dabigatran · Atrial fibrillation · Elderly

Abstract

Introduction: In patients with atrial fibrillation (AF) at risk for stroke, dabigatran 150 mg twice a day (DE150) is superior to warfarin for stroke prevention. However, there is paucity of data with respect to bleeding risk at this dose in elderly patients (≥ 75 years). We aimed to evaluate the safety of DE150 in comparison to warfarin in a real-world population with AF and low bleeding risk (HAS-BLED score ≤ 2). **Methods:** In this prospective observational study, 754 consecutive patients with AF and HAS-BLED score ≤ 2 were included. We compared outcome of elderly patients (age ≥ 75 years) to younger patients (age < 75 years). The primary end point was the combined incidence of all-cause mortality, stroke, systemic emboli, and major bleeding event during a mean follow-up of 1 year. **Results:** There were 230 (30%) elderly patients, 151 patients were treated with warfarin, and 79 were treated with DE150. Fifty-two patients experienced the primary end-point during the 1-year follow-up. Among the elderly, at 1-year of follow-up, the cumulative event rate of the com-

bined endpoint in the DE150 and warfarin was 8.9 and 15.9% respectively ($p = 0.14$). After adjustment for age and gender, patients who were treated with DE150 had a nonsignificant difference in the risk for the combined end point as patients treated with warfarin both among the elderly and among the younger population (HR 0.58, 95% C.I. = 0.25–1.39 and HR = 1.12, 95% C.I. 0.62–2.00, respectively [p for age-group-by-treatment interaction = 0.83]). **Conclusions:** Our results suggest that Dabigatran 150 mg twice a day can be safely used among elderly AF patients with low bleeding risk.

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Introduction

In patients with nonvalvular atrial fibrillation (AF), high-dose (150 mg twice a day) dabigatran is considered to be superior to warfarin with respect to preventing stroke and systemic embolism whereas low dose (110 mg twice a day) dabigatran is associated with a lower bleeding risk compared with warfarin [1]. Elderly patients (≥ 75 years) are less represented in randomized clinical trials and the appropriate dabigatran dosage that should be uti-

Table 1. Baseline characteristics by treatment

	Age <75 years			Age ≥75 years		
	warfarin	DE150	<i>p</i> value	warfarin	DE150	<i>p</i> value
<i>N</i>	239	285		151	79	
Demographic information						
Gender, male %	56	70	0.01	48	48	0.97
Age	65±9	64±9	0.34	80±2.8	79±2.7	0.01
Lab Tests						
GFR, mL/min	91±27	86±28	0.03	77±22	78±21	0.60
Hemoglobin, g/dL	13±1.9	13±1.8	0.01	12±2.3	13±1.6	0.13
Past medical history						
CHF	19	16	0.30	35	14	0.34
Diabetes mellitus	11	24	0.01	27	16	0.66
Hypertension	40	46	0.13	41	52	0.12
PVD	3	1	0.03	1	1	0.97
Past PE	1	2	0.46	2	1	0.69
Past DVT	2	1	0.30	1	1	0.65
Liver dysfunction	1	1	0.89	0	3	0.05
Coronary artery disease	23	24	0.82	23	28	0.37
Past TIA/Stroke	8	20	0.01	15	22	0.23
History of major bleeding	2	2	0.94	2	1	0.69
Drug/Alcohol abuse	4	1	0.02	1	3	0.51
HAS-BLED score	1.5±0.8	1.6±1.0	0.29	1.9±0.7	2.1±0.8	0.02
CHA2DS2-VASc	2.2±1.3	2.4±1.6	0.07	4.1±1.4	4.2±1.4	0.75
Medication prior to enrollment						
Aspirin	24	23	0.79	24	29	0.39
Clopidogrel	7	5	0.38	6	3	0.25

Data are presents as the mean ± SD or percentages.

lized among this population is not clear. Some experts suggest that the lower dose should be used in elderly patients [2]. We aimed to analyze real-world data from a prospective observational study on elderly and younger AF patients with a low bleeding risk (HAS-BLED score ≤2) and compare the safety and effectiveness of dabigatran 150 mg bid (DE150) and warfarin during 1-year follow-up.

Methods

This is a multicenter prospective cohort study including consecutive patients with AF and low HAS-BLED score. Patients were enrolled between March 2016 and November 2018 from 10 medical centers in Israel. Patients were included in this study if they were prescribed dabigatran 150 mg bid or warfarin according to treating physician discretion, had a HAS-BLED score ≤2, and an estimated eGFR >50 mL/min. Patients were excluded if they had a life expectancy <12 months, were prescribed potent P-gp inhibitors, had a mechanical valve, moderate or severe mitral stenosis, or advanced hepatic dysfunction. Patients were followed up for 1 year after enrollment; follow-up data were obtained by phone inter-

views, patients visit, and screening of medical records. Data was collected using a secured web-based questionnaire developed by the study coordination center at the Israeli Center for cardiovascular Research.

The primary endpoint was a composite of all-cause mortality, major bleeding event, systemic emboli, and stroke. Secondary outcomes included the separate components of the primary outcome. Secondary outcomes should be considered as hypothesis generating only.

Baseline characteristics of study patients were compared with the *t*-test for continuous variables and the χ^2 test for categorical variables. Continuous variables are presented as mean ± SD and categorical variables are presented as proportions. The cumulative probability of the primary endpoint was graphically displayed according to the method of Kaplan and Meier, with comparison of cumulative events by the log-rank test.

Cox proportional-hazard regression modeling adjusting for age (continuous) and gender was performed to estimate the risk for the primary endpoint associated with treatment. The proportional-hazards assumptions were verified with the use of Schoenfeld residuals. Interaction *p* values were computed and reported between treatment groups and the effect of age on endpoints. All *p* values are 2-tailed. Analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC, USA).

Fig. 1. Kaplan-Meier estimates of cumulative probability for the primary end point (all-cause mortality, stroke, systemic emboli, and major bleeding event) by treatment among younger patients (**a**) and the elderly patients (**b**).

Results

The cohort of this study included 754 AF patients, 312 (41%) of them were women. There were 230 patients classified as elderly (Age ≥ 75 years) and 524 as younger (Age < 75 years) patients. Among the elderly, 151 (66%) patients were treated with warfarin and 79 (34%) patients were treated with DE150.

The clinical characteristics of the study patients by age and treatment groups are shown in Table 1. The proportion of males was higher in the DE150 as compared to the warfarin group among the younger population but not among the elderly.

Among the younger population, those that were treated with DE150 were more likely to have diabetes mellitus and previous stroke versus those who were treated with warfarin. Baseline characteristics among the elderly patients were comparable for those who were treated with

DE150 and those who were treated with Warfarin. During 1-year follow-up, 52 patients (7%) experienced the combined endpoint of death, major bleeding event, systemic emboli, or stroke.

The cumulative probability of the combined endpoint in patients treated with DE150 versus warfarin among the elderly and among the younger is shown in Figure 1a, b, respectively. The cumulative 1-year event rates for each endpoint are presented in Table 2.

In a multivariate analysis adjusting for age and gender, there was a nonsignificant difference in the risk of the combined endpoint between elderly patients treated with DE150 compared with elderly patients treated with warfarin (HR 0.58, C.I. = 0.25–1.39, p value = 0.22). The risk for the combined end point was nonsignificantly different between younger patients who were treated with DE150 and younger patients who were treated with warfarin (HR = 1.12, C.I. = 0.62–2.0, p value = 0.71). Accord-

Table 2. One-year outcomes by treatment

	Age <75 years			Age ≥75 years		
	warfarin	DE150	<i>p</i> value	warfarin	DE150	<i>p</i> value
<i>N</i>	239	289		151	79	
Stroke/systemic embolism, %	0	1.4	0.07	0	2.5	0.050
Major bleeding, %	0.4	0.7	0.67	0.7	0	0.47
Mortality, %	7.9	8.4	0.85	15.2	7.6	0.10
Composite end point,* %	8.4	9.5	0.66	15.9	8.9	0.14

* Composite endpoint includes: mortality, stroke, systemic embolism, and major bleeding.

ingly, the interaction between age-group and treatment regimen was nonsignificant (p for age-group-by-treatment interaction = 0.83). In a sensitivity analysis including the following variables in the multivariate models: age, gender, heart failure, diabetes mellitus, GFR; the results were consistent showing that the risk of the combined endpoint was nonsignificantly different in the elderly DE150 and elderly warfarin groups (HR = 0.58, p = 0.22) as well as in the younger DE150 and younger warfarin groups (HR = 0.89, p = 0.71), p for interaction = 0.61.

Discussion

In this study, among patients with AF who have low bleeding risk (HAS-BLED ≤2), treatment with DE150 as compared to warfarin was not associated with higher adverse effects in either the elderly or among the younger patients. Administering of dabigatran 150 mg twice daily is more effective in reducing absolute stroke risk than administration of dabigatran 110 mg twice daily [1, 3]. However, among patients considered to be at high risk for bleeding, a lower dose of dabigatran may be safer [4]. In a post hoc analysis of the RE-LY trial, There was a significant treatment-by-age interaction, such that dabigatran 150 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years (2.12 vs. 3.04%; p < 0.001) and a trend toward higher risk of major bleeding in those aged ≥75 years (5.10 vs. 4.37%; p = 0.07; p for interaction <0.001) [5]. However, in this analysis, the risk for bleeding was not reported.

The European Society of Cardiology Practical Guide on the use of NOACs in patients with AF recommends considering the lower dose of dabigatran in the elderly [2, 6]. However, in addition to age and sex, there are several other important predictors for major bleeding, and

the risk increases with dabigatran in both doses. In a recent analysis from the RE-LY trial, Stam-Slob et al. [7] developed an estimation model for the absolute benefit and harm from treatment with dabigatran in individual patients with AF that can aid in selection of the optimal dose for each individual. In a recent meta-analysis, Sharma et al. [6] investigated the safety and efficacy of dabigatran compared to warfarin in elderly patients with AF or venous thromboembolism. In this study, DE150 treatment was associated with a significant reduction in the risk of stroke and systemic embolism in comparison to warfarin, but there was a nonsignificant higher risk of major bleeding observed with DE150 treatment [6]. Our results support previous studies and suggesting that individualized dose selection is appropriate especially among the elderly AF population and add important data on the safety of treatment with dabigatran 150 mg twice a day among elderly patients with a low bleeding risk.

Our study has several limitations. It is based on a prospective registry and the choice of drug was made by the discretion of the treating physician, but we have adjusted our model to reflect the different baseline characteristics among the treatment groups. Our results are limited also by the relatively small population and events throughout the follow-up period. We did not collect data regarding drug-compliance nor INR values during follow-up, and thus, we could not report Time in Therapeutic Range for patients treated with warfarin.

In conclusion, our study shows that in patients with AF and low bleeding risk (HAS-BLED ≤2), treatment with dabigatran 150 mg twice a day is safe at least as warfarin in both elderly and younger patients. Current practice that limits dabigatran use in elderly patients should be reconsidered and in particular, administration of high-dose dabigatran for the elderly population should not be avoided based solely on age.

Statement of Ethics

The study was approved by the Ethics Committees of all participating centers. All patients provided written informed consent for the collection of data and subsequent analysis. Reference numbers of the ethics committees are 0187-18-TLV, 0155-18-RMC, 0171-18-RMC, 0036-18-BRZ, 0027-18-WOMC, 0049-18-MMC, 0013-18-POR, 0020-18-POR, 0217-17-KMC, 326-18-RMB, 4139-17-SMC, 0033-18-ZIV, 0389-18-RMC.

Conflict of Interest Statement

A. Barsheshet and R. Klempfner have received speaker honoraria from Boehringer Ingelheim, Pfizer, and Bayer. G. Golovchiner, E. Kadmon, G. Goldenberg, and A. Erez have nothing to declare.

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: A.E. and A.B.; data collection: R.K., I.G. and G.G.; analysis and interpretation of results: A.E. and A.B.; draft manuscript preparation: A.E. All authors reviewed the results and approved the final version of the manuscript.

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