ORIGINAL RESEARCH ARTICLE

Effects of dabigatran according to age in atrial fibrillation

Mandy N Lauw,[1,2] John W Eikelboom,[1] Michiel Coppens,[1,2] Lars Wallentin,[3] Salim Yusuf,[1] Michael Ezekowitz,[4,5] Jonas Oldgren,[3] Juliet Nakamya,[1] Jia Wang,[1] Stuart J Connolly[1]

[1]McMaster University and Hamilton Health Sciences, Population Health Research Institute, Hamilton, Ontario, Canada
[2]Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
[3]Department of Medical Sciences, Clinical Research Center, University of Uppsala, Uppsala, Sweden
[4]Jefferson Medical College and Lankenau Medical Center, Philadelphia, Pennsylvania, USA
[5]Cardiovascular Research Foundation, New York, New York, USA

Correspondence to
Mandy N Lauw, Population Health Research Institute, Hamilton Health Sciences, General Hospital 237 Barton Street East, Hamilton, ON L8L 2X2, Canada; mandy.lauw@phri.ca

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ABSTRACT

Objective The prevalence of atrial fibrillation (AF) and the risk of stroke and bleeding vary according to age. To estimate effects of dabigatran, compared with warfarin, on stroke, bleeding and mortality in patients with AF in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial according to age, we analysed treatment effects using age as a continuous variable and using age categories.

Methods RE-LY included 10 855 (59.9%) patients aged <75 years, 4231 patients (23.4%) aged 75–79 years, 2305 (12.7%) aged 80–84 years and 722 (4.0%) aged ≥85 years at baseline.

Results Benefits of dabigatran versus warfarin regarding stroke (HR range 0.63 (95% CI 0.46 to 0.86) to 0.70 (0.31 to 1.57) for dabigatran 150 mg twice daily), HR range 0.52 (0.21 to 1.29) to 1.08 (0.73 to 1.60) for dabigatran 110 mg twice daily) and intracranial bleeding were maintained across all age groups (interaction p values all not significant). There was a highly significant interaction (p value interaction <0.001) between age and treatment for extracranial major bleeding, with lower rates with both doses of dabigatran compared with warfarin in younger patients (HR 0.78 (0.62 to 0.97) for 150 mg twice daily, HR 0.72 (0.57 to 0.90) for 110 mg twice daily) but similar (HR 1.50 (1.03 to 2.18) for 110 mg twice daily) or higher rates (HR 1.68 (1.18 to 2.41) for 150 mg twice daily) in older patients (≥80 years).

Conclusion Effects of dabigatran compared with warfarin on stroke prevention and intracranial bleeding are consistent across all age groups. Effects of dabigatran on extracranial major bleeding are age dependent, supporting selection of dabigatran 110 mg twice daily for elderly patients (age ≥80 years).

Trial registration number Clinical trial registration number: https://clinicaltrials.gov NCT00262600.

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INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia and a leading cause of stroke.[1 2] The prevalence of AF increases with advancing age, rising from <1% in persons aged 55–59 years to >10% in those aged ≥85 years.[3 4] The absolute risk of stroke with AF also increases with advancing age,[2 5] emphasizing the need for effective stroke prevention in the older AF population. Vitamin K antagonists reduce stroke risk in AF patients by approximately two-thirds compared with the placebo.[6] However, older persons with AF are undertreated, most often because clinicians are concerned about the risk of bleeding.[7–9]

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial involving 18 113 patients with AF demonstrated that dabigatran etexilate (hereafter referred to as dabigatran) 150 mg twice daily was superior to warfarin for stroke or non-central nervous system (non-CNS) systemic embolism prevention, produced a similar rate of major bleeding and extracranial bleeding and was associated with a reduction in intracranial bleeding and cardiovascular mortality. Dabigatran 110 mg twice daily was non-inferior to warfarin for stroke or non-CNS systemic embolism prevention and was associated with a reduction in major and intracranial bleeding.[10] In a previous paper, we analysed bleeding rates according to an age cut-off of 75 years and reported a reduction in intracranial bleeding in older and younger patients with both doses of dabigatran, while extracranial major bleeding was lower with both doses of dabigatran compared with warfarin in younger patients and similar or higher in older patients.[11]

In the present paper, we seek to better characterise the effects of dabigatran compared with warfarin on stroke, bleeding and mortality rates with analyses using age as a continuous variable and according to additional age groups.

METHODS

Trial design and study population

Details of the RE-LY trial design and population have been published previously.[10] Briefly, the trial was designed to establish the non-inferiority of dabigatran 110 or 150 mg twice daily compared with dose-adjusted warfarin (target international normalised ratio (INR) 2.0 to 3.0) for stroke prevention in patients with AF and at least one additional risk factor for stroke. The primary efficacy outcome was stroke or non-CNS systemic embolism, and the main safety outcome was major bleeding. The mean duration of follow-up was 2.0 years, with a maximum follow-up of up to 3 years.[10] The study was approved by all appropriate national regulatory authorities and ethics committees of the participating centres and performed in accordance with the Declaration of Helsinki (ClinicalTrials.gov trial registration number NCT00262600).

Statistical analysis

All analyses were conducted according to the intention-to-treat principle. Patient baseline

characteristics were summarised in patients aged <75, 75–79, 80–84, and ≥85 years as mean±SD for continuous variables and as frequencies and percentages for categorical variables. These age groups were defined post hoc in part on clinical interest and in alignment with current recommendations of some health authorities. Differences in baseline characteristics were tested using analysis of variance for continuous variables and Pearson's χ^2 tests for categorical variables. Outcome events were observed from randomisation until the end of the study, loss to follow-up or death.

We examined the effects of dabigatran 110 mg twice daily, dabigatran 150 mg twice daily and warfarin on the risk of outcome events in the age subgroups (<75, 75 to <80, 80 to <85 and ≥85 years) separately using Cox proportional-hazards regression and reported the results as HR and 95% CI. The interaction effect of treatment and age was assessed by Wald's test for interaction term in the Cox model for continuous age, as well as for the age groups. The treatment-by-age interaction effect on risk of outcomes was further explored by non-parametric subpopulation treatment effect pattern plots (STEPPs).[12 13] The sliding-window approach was applied to create overlapping subpopulations within each treatment arm according to baseline age. The number of patients in each subpopulation and the number of overlapping patients between consecutive subpopulations were set to 1000 and 900, respectively. These numbers were artificially based on the total amount of patients in the RE-LY study, and the same group sizes were used for each outcome event. The annual risk rate was calculated for each subpopulation and plotted against the corresponding median age value. A LOESS (locally weighted scatter-plot smoothing) smooth curve was thereafter fitted to the risk rates for each treatment arm to illustrate the overall trend between age and risk of outcome events.[14] All analyses were performed using SAS software V.9.2 (SAS Institute, Cary, NC). A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The RE-LY trial randomised 18 113 patients with AF and at least one additional risk factor for stroke. There were 10 855 (59.9%) patients aged <75 years, 4231 patients (23.4%) aged 75–79 years, 2305 (12.7%) aged 80–84 years and 722 (4.0%) aged ≥85 years at baseline. Baseline characteristics for each age category are presented in table 1. Patients over age 75 were more often women and had a lower mean body weight, higher mean $CHADS_2$ score and poorer renal function, as estimated by creatinine clearance calculated according to the Cockcroft-Gault method. With advancing age, patients were also more likely to have AF on baseline electrocardiogram and a history of stroke or transient ischaemic attack (TIA) (table 1).

Event rates according to age

Risks of outcome event rates according to treatment arm, stratified by the four age categories, are provided in table 2. Table 2 also shows the p values for interaction between treatment and age, calculated with age as a continuous variable primarily, and according to the age categories. Event rates for all clinical outcomes increased with advancing age in each treatment arm. Treatment effects of dabigatran versus warfarin regarding the primary efficacy outcome, stroke or non-CNS systemic embolism, were consistent across all ages and age groups (HR ranging from 0.63 [95% CI 0.46 to 0.86] in patients <75 years to 0.70 (95% CI 0.31 to 1.57) in patients ≥85 years for dabigatran 150 mg twice daily, HR ranging from 0.93 (95% CI 0.70 to 1.22) in patients <75 years to 0.52 (95% CI 0.21 to 1.29) in patients ≥85 years for dabigatran 110 mg twice daily; interaction p values all not significant). Estimates of effect on stroke were consistently in favour of dabigatran 150 mg twice daily across the full age spectrum. There was a significant interaction between age and treatment for both doses of dabigatran compared with warfarin for major bleeding, with lower rates with both doses of dabigatran in younger patients <75 years of age (HR 0.70 (95% CI 0.57 to 0.86) for dabigatran 150 mg twice daily, HR 0.62 (95% CI 0.50 to 0.77) for dabigatran 110 mg twice daily) but similar (110 mg twice daily; HR 1.18 (95% CI 0.84 to 1.65)) or higher rates (150 mg twice daily; HR 1.41 (95% CI 1.02 to 1.94)) in older patients (aged ≥80 years). However, based on the analysis of the site of bleeding, it was clear that this is driven completely by a strong treatment–age interaction related to extracranial major bleeding (as distinct from intracranial bleeding), with lower rates under treatment with both doses of dabigatran in younger patients (<75 years; HR 0.78 (95% CI 0.62 to 0.97) for dabigatran 150 mg twice daily, HR 0.72 (95% CI 0.57 to 0.90) for dabigatran 110 mg twice daily) but similar (HR 1.50 (95% CI 1.03 to 2.18) for dabigatran 110 mg twice daily) or higher rates (HR 1.68 (95% CI 1.18 to 2.41) for dabigatran 150 mg twice daily) in older patients (aged ≥80 years). Interactions between age and treatment for extracranial major bleeding also remained significant after substratification of the age groups by renal function (appendix table 1).

For intracranial bleeding, there were reductions in both doses of dabigatran compared with warfarin in both younger and older patients (HR ranging from 0.43 (95% CI 0.25 to 0.74) in patients <75 years to 0.61 (95% CI 0.20 to 1.87) in patients ≥85 years for dabigatran 150 mg twice daily, HR ranging from 0.22 (95% CI 0.11 to 0.45) in patients <75 years to 0.13 (95% CI 0.02 to 1.04) in patients ≥85 years for dabigatran 110 mg twice daily). There was also evidence of an age interaction for the effect of both doses of dabigatran (compared with warfarin) on all-cause mortality (interaction p values 0.026 and 0.014). Both doses of dabigatran reduced mortality at lower ages (<75 years; HR 0.77 (95% CI 0.64 to 0.93) for dabigatran 150 mg twice daily, HR 0.82 (95% CI 0.68 to 0.98) for dabigatran 110 mg twice daily), with mortality at higher ages being similar between dabigatran and warfarin (≥85 years; HR 1.15 (95% CI 0.74 to 1.79) for dabigatran 150 mg twice daily, HR 1.37 (95% CI 0.89 to 2.11) for dabigatran 110 mg twice daily).

Subpopulation treatment effect pattern plots

The STEPPs show the relationship between increasing age and treatment effects in a visual manner (figures 1–5). For stroke or non-CNS systemic embolism, event rates were consistently lower for dabigatran 150 mg twice daily and similar or lower for dabigatran 110 mg twice daily compared with warfarin across the entire age spectrum (figure 1). For major bleeding, event rates were lower with both doses of dabigatran compared with warfarin in younger patients, with a gradual reversal with increasing age (>77 years for dabigatran 150 mg twice daily and >80 years for dabigatran 110 mg twice daily; figure 2). Figures 3 and 4 visually show the striking difference between intracranial and extracranial bleeding with respect to the age–treatment interaction. For extracranial major bleeding,[4] rates with dabigatran were lower at younger ages, but the curves cross during the eighth decade (>74 years for dabigatran 150 mg twice daily and >76 years for dabigatran 110 mg twice daily). For intracranial bleeding,[3] rates were much lower across all ages with

Table 1 Patient characteristics at baseline according to age groups

	Age group (years)				
	<75	≥75 to <80	≥80 to <85	≥85	p value*
Total number of patients	10 855	4231	2305	722	
Male sex, n (%)	7318 (67.4)	2518 (59.5)	1296 (56.2)	382 (52.9)	<0.0001
Age (years), mean±SD	66.2±6.9	76.8±1.4	81.7±1.4	86.8±2.2	N/A
Systolic blood pressure (mmHg), mean±SD	130±17.5	132±17.4	132±17.2	131±17.3	<0.0001
Body weight (kg), mean±SD	86.3±20.9	78.8±16.5	76.4±15.6	71.7±14.0	<0.0001
eGFR, mean±SD	82.9±42.3	62.3±17.9	54.7±20.1	45.8±12.2	<0.0001
eGFR <50 mL/min, n (%)	941 (8.7)	1034 (24.4)	996 (43.2)	492 (68.1)	<0.0001
eGFR 50 to ≤80 mL/min, n (%)	4714 (43.4)	2556 (60.4)	1148 (49.8)	224 (31.0)	<0.0001
eGFR >80 mL/min, n(%)	5190 (47.8)	363 (15.0)	160 (6.9)	6 (0.8)	<0.0001
Type of AF					
Persistent, n (%)	3436 (31.7)	1345 (31.8)	761 (33.0)	247 (34.2)	0.3425
Paroxysmal, n (%)	3617 (33.3)	1377 (32.5)	724 (31.4)	225 (31.2)	0.2190
Permanent, n (%)	3797 (35.0)	1508 (35.6)	820 (35.6)	250 (34.6)	0.8445
AF first diagnosis >2 years, n (%)	5161 (47.5)	2008 (47.5)	1016 (44.1)	310 (42.9)	0.0024
AF on baseline ECG, n (%)	7786 (71.7)	3136 (74.1)	1724 (74.8)	578 (80.1)	<0.0001
$CHADS_2$ score, mean±SD	1.85±1.0	2.57±1.1	2.58±1.1	2.67±1.1	<0.0001
0 or 1, n (%)	4731 (43.6)	635 (15.0)	325 (14.1)	84 (11.6)	<0.0001
2, n (%)	3461 (31.9)	1729 (40.9)	968 (42.0)	297 (41.1)	<0.0001
>2, n (%)	2662 (24.5)	1867 (44.1)	1012 (43.9)	341 (47.2)	<0.0001
CHA_2DS_2–VASc score, mean±SD	3.15±1.2	4.23±1.4	4.28±1.3	4.40±1.4	<0.0001
0 or 1, n (%)	630 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)	<0.0001
2, n (%)	2880 (26.5)	328 (7.8)	161 (7.0)	39 (5.4)	<0.0001
>2, n (%)	7344 (67.7)	3903 (92.2)	2144 (93.0)	683 (94.6)	<0.0001
Risk factors for stroke					
Previous stroke or TIA, n (%)	2266 (20.9)	767 (18.1)	430 (18.7)	160 (22.2)	0.0002
Heart failure, n (%)	3946 (36.4)	1026 (24.2)	599 (26.0)	222 (30.7)	<0.0001
Hypertension, receiving treatment, n (%)	8810 (81.2)	3182 (75.2)	1750 (75.9)	541 (74.9)	<0.0001
Diabetes mellitus, n (%)	2774 (25.6)	898 (21.2)	426 (18.5)	123 (17.0)	<0.0001
Previous myocardial infarction, n (%)	1753 (16.1)	712 (16.8)	409 (17.7)	131 (18.1)	0.1601
Peripheral arterial disease, n (%)	351 (3.2)	176 (4.2)	108 (4.7)	46 (6.4)	<0.0001
Coronary artery disease, n (%)	2955 (27.2)	1209 (28.6)	675 (29.3)	195 (27.0)	0.1213
Valvular heart disease, n (%)	2132 (19.6)	977 (23.1)	629 (27.3)	206 (28.5)	<0.0001
Concomitant medications at baseline					
Aspirin, n (%)	4356 (40.1)	1621 (38.3)	920 (39.9)	301 (41.7)	0.1667
ARB or ACE inhibitor, n (%)	7537 (69.4)	2625 (62.0)	1401 (60.8)	416 (57.6)	<0.0001
Beta blocker, n (%)	7169 (66.0)	2517 (59.5)	1317 (57.1)	372 (51.5)	<0.0001
Amiodarone, n (%)	1294 (11.9)	394 (9.3)	190 (8.2)	55 (7.6)	<0.0001
PPI or H2 receptor antagonist, n (%)	1716 (15.8)	752 (17.8)	516 (22.4)	160 (22.2)	<0.0001
On OAC at time of randomisation, n (%)	6782 (62.5)	2651 (62.7)	1360 (59.0)	396 (54.8)	<0.0001

*Null hypothesis of no difference: categorical variables compared using the χ^2, continuous variables using analysis of variance.
AF, atrial fibrillation; ARB, angiotensin receptor blocker; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; OAC, oral anticoagulation; PPI, proton-pump inhibitor; TIA, transient ischemic attack.

dabigatran than with warfarin. These effects of dabigatran on intracranial bleeding remained similar in a sensitivity analysis for patients with aspirin use at baseline (online supplementary figures 1 and 2). Mortality was lower with both doses of dabigatran compared with warfarin in younger patients, with gradual loss of this effect with increasing age, especially over the age of 75, where death rates between dabigatran and warfarin were comparable (figure 5).

DISCUSSION

There is considerable interest in understanding the effects of oral anticoagulants across the spectrum of age, as the risk of stroke and bleeding are quite different between older and younger patients, and there are also differences in drug metabolism and comorbidities. In this paper, we have presented data according to age, analysing age as a continuous variable and showing specific subgroups of old and very old patients of special interest. One main finding was that the effects of both doses of dabigatran compared with warfarin for reduction of stroke and systemic embolism are highly consistent across all age groups. This is shown by the lack of statistical interaction in the subgroup analysis and the observation of consistent benefit of dabigatran 150 mg twice daily in the STEPPs of stroke or non-CNS systemic embolism rates across the full age spectrum.

To understand the effect of age on major bleeding, we need to separate intracranial and extracranial bleeding, because they behave very differently. There is a strong interaction between age and the effect of dabigatran compared with warfarin for

Table 2 Risk of clinical outcome events stratified by age categories

		Dabigatran 110 mg (n=6015)		Dabigatran 150 mg (n=6076)		Warfarin (n=6022)		Dabigatran 110 mg versus warfarin			Dabigatran 150 mg versus warfarin		
Clinical outcome	Age	Number of events	Event Rate (%/year)	Number of events	Event rate (%/year)	Number of events	Event rate (%/year)	HR (95% CI)	p value for interaction (age groups)*	p value for interaction (age continuous)	HR (95% CI)	p value for interaction (age groups)*	p value for interaction (age continuous)
Stroke/Non-CNS systemic embolism	<75, n=10 855	96	1.32	65	0.90	101	1.43	0.93 (0.70 to 1.22)	0.394	0.253	0.63 (0.46 to 0.86)	0.996	0.498
	75–79, n=4231	52	1.90	32	1.14	49	1.76	1.08 (0.73 to 1.60)			0.65 (0.42 to 1.01)		
	80–84, n=2305	28	1.95	27	1.73	38	2.58	0.75 (0.46 to 1.23)			0.67 (0.41 to 1.10)		
	≥85, n=722	7	1.61	10	2.15	14	3.09	0.52 (0.21 to 1.29)			0.70 (0.31 to 1.57)		
Major bleeding	<75, n=10 855	138	1.89	153	2.12	215	3.04	0.62 (0.50 to 0.77)	0.006	<0.001	0.70 (0.57 to 0.86)	0.001	<0.001
	75–79, n=4231	106	3.87	120	4.28	116	4.16	0.93 (0.71 to 1.21)			1.04 (0.81 to 1.35)		
	80–84, n=2305	72	5.01	92	5.91	63	4.28	1.18 (0.84 to 1.65)			1.41 (1.02 to 1.94)		
	≥85, n=722	26	6.00	34	7.29	27	5.96	1.01 (0.59 to 1.73)			1.22 (0.74 to 2.02)		
Intracranial major bleeding	<75, n=10 855	10	0.14	19	0.26	43	0.61	0.22 (0.11 to 0.45)	0.347	0.667	0.43 (0.25 to 0.74)	0.481	0.548
	75–79, n=4231	11	0.40	5	0.18	22	0.79	0.51 (0.25 to 1.04)			0.23 (0.09 to 0.60)		
	80–84, n=2305	5	0.35	10	0.64	17	1.16	0.30 (0.11 to 0.82)			0.55 (0.25 to 1.21)		
	≥85, n=722	1	0.23	5	1.07	8	1.77	0.13 (0.02 to 1.04)			0.61 (0.20 to 1.87)		
Extracranial major bleeding	<75, n=10 855	128	1.76	137	1.90	173	2.44	0.72 (0.57 to 0.90)	0.004	<0.001	0.78 (0.62 to 0.97)	0.001	<0.001
	75–79, n=4231	96	3.51	115	4.11	95	3.41	1.03 (0.78 to 1.37)			1.22 (0.93 to 1.61)		
	80–84, n=2305	68	4.73	82	5.27	47	3.20	1.50 (1.03 to 2.18)			1.68 (1.18 to 2.41)		
	≥85, n=722	25	5.77	29	6.22	20	4.41	1.32 (0.73 to 2.38)			1.41 (0.80 to 2.49)		
All-cause mortality	<75, n=10 855	206	2.83	192	2.66	245	3.46	0.82 (0.68 to 0.98)	0.088	0.026	0.77 (0.64 to 0.93)	0.068	0.014
	75–79, n=4231	105	3.84	103	3.68	124	4.45	0.86 (0.66 to 1.11)			0.82 (0.63 to 1.07)		
	80–84, n=2305	87	6.05	100	6.42	82	5.57	1.09 (0.80 to 1.47)			1.16 (0.87 to 1.55)		
	≥85, n=722	48	11.07	43	9.23	36	7.95	1.37 (0.89 to 2.11)			1.15 (0.74 to 1.79)		

There were 10 855, 4231, 2305 and 722 patients in the age categories of<75, 75–79, 80–84 and≥85 years; respectively.
*p Value for interaction is from Wald's test of interaction between age and treatment.
CNS, central nervous system.

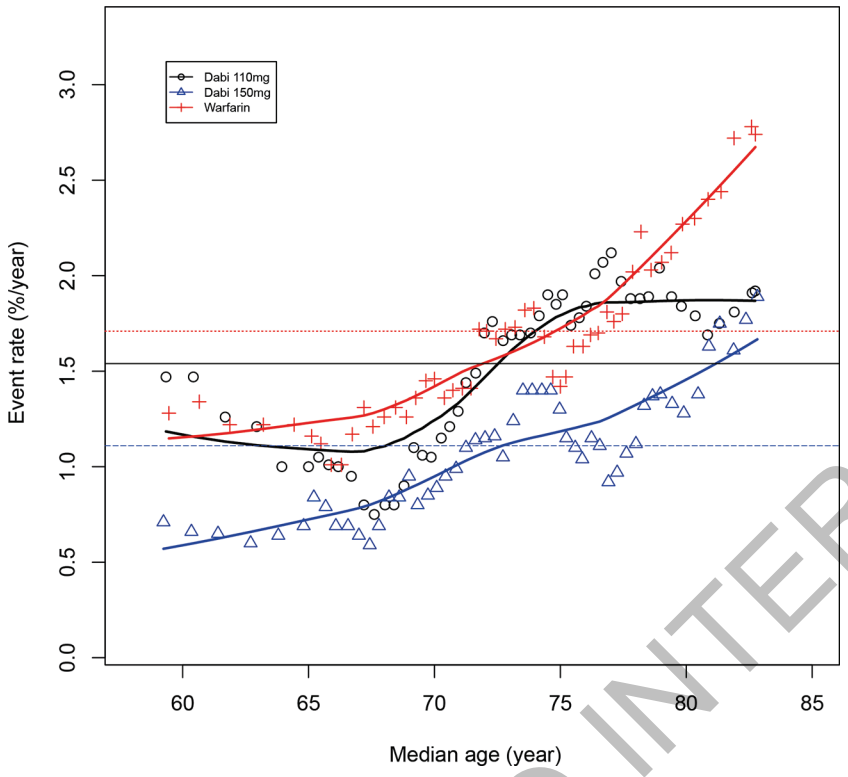

Figure 1 Subpopulation treatment effect pattern plot (STEPP) according to baseline age for stroke /non-central nervous system systemic embolism.

extracranial major bleeding. The interaction p values and the plots showing extracranial bleeding rates of dabigatran and warfarin demonstrate this both mathematically and visually. There is a strong advantage of both doses of dabigatran compared with warfarin with respect to extracranial bleeding in younger patients, which diminishes with increasing age and eventually reverses for the higher dabigatran dose, particularly for patients in the eighth decade. Although the age–treatment interaction is similar for both dabigatran doses, the warfarin plot crosses that of dabigatran at a higher age when the dabigatran dose is lower (>74 years for dabigatran 150 mg twice daily versus >76 years for dabigatran 110 mg twice daily). On the other hand, for

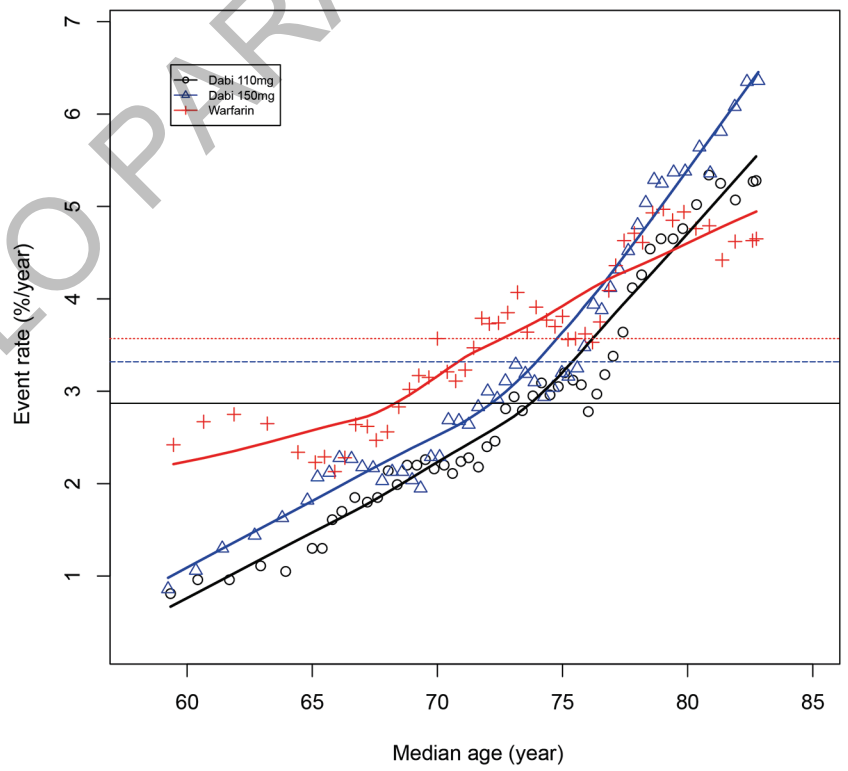

Figure 2 Subpopulation treatment effect pattern plot (STEPP) according to baseline age for major bleeding.

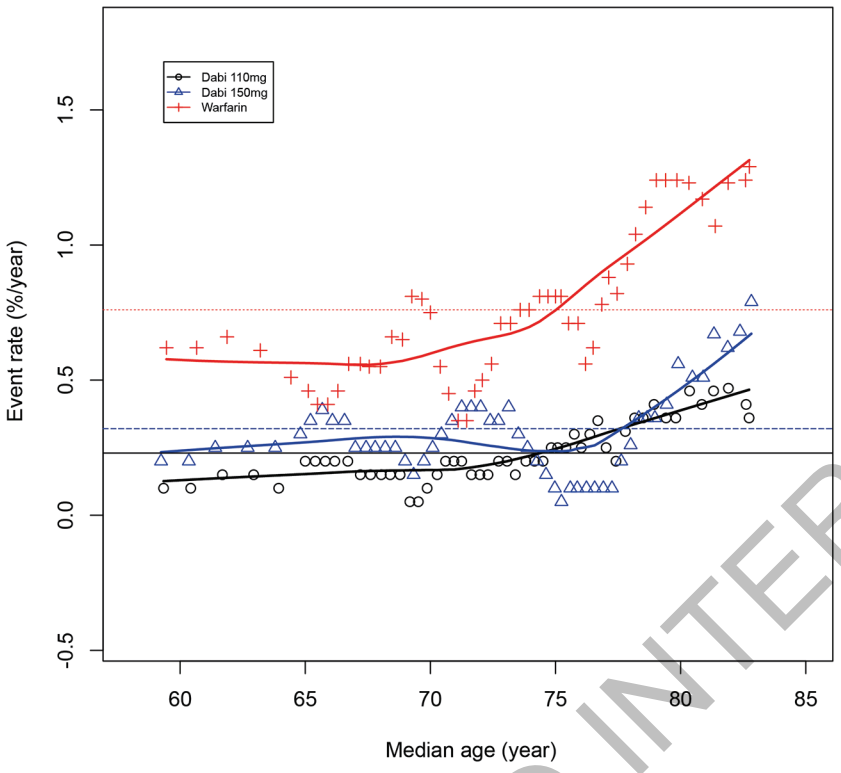

Figure 3 Subpopulation treatment effect pattern plot (STEPP) according to baseline age for intracranial bleeding.

intracranial bleeding, there is a substantial benefit of both doses of dabigatran compared with warfarin across the entire age spectrum, with no suggestion of an age interaction.

In two recent meta-analyses, the marked benefit for intracranial bleeding was confirmed for dabigatran, as well as the other direct oral anticoagulants (DOACs) in comparison with vitamin K antagonists,[15 16] and this benefit remained in elderly patients.[16] The latter meta-analysis also indicates an increased risk of gastrointestinal bleeding in the elderly with all DOACs.[16] On the contrary, a recent real-world study suggested an increased risk of extracranial bleeding with dabigatran compared with warfarin in all patients, irrespective of age.[17] This is contrary to our

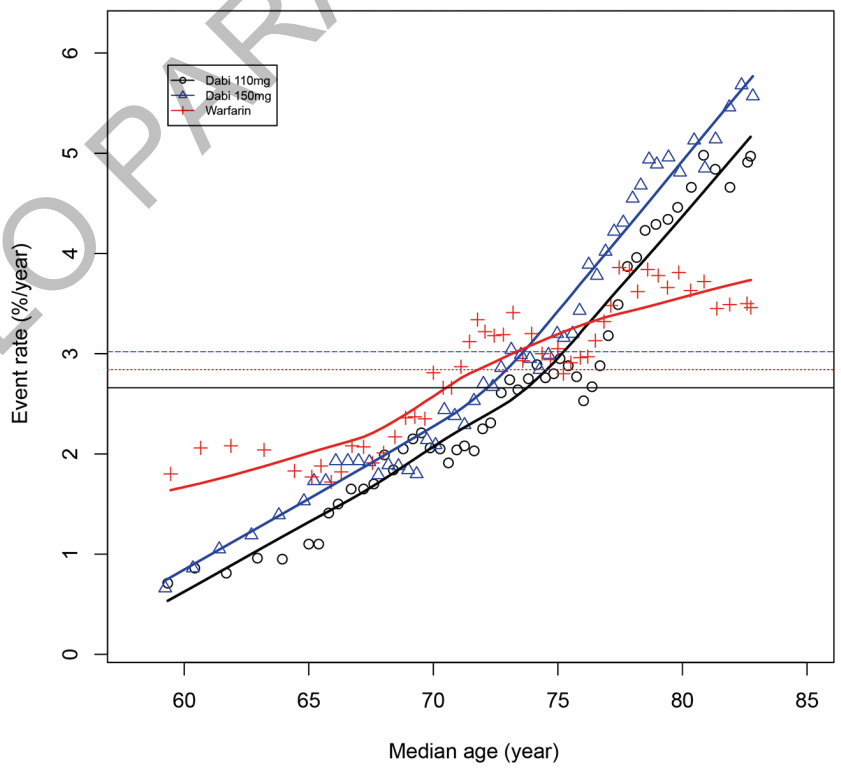

Figure 4 Subpopulation treatment effect pattern plot (STEPP) according to baseline age for extracranial major bleeding.

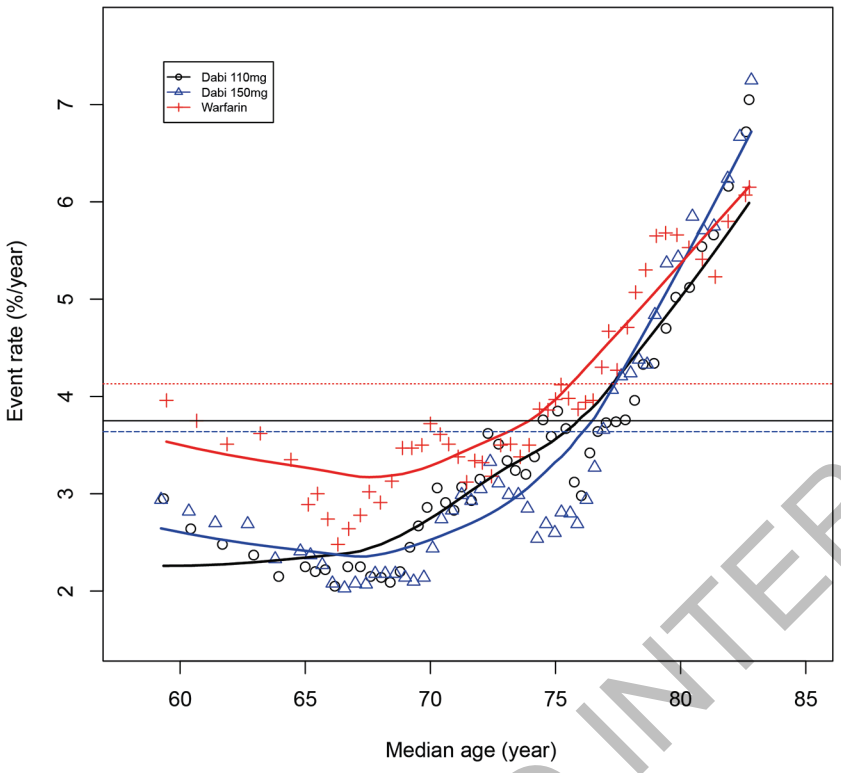

Figure 5 Subpopulation treatment effect pattern plot (STEPP) according to baseline age for all-cause mortality.

data and the aforementioned meta-analysis,[16] as well as a previously published FDA study and a Danish registry.[18 19] This may be explained by the fact that this real-world study did not differentiate between the two dosages of dabigatran, that there was no adjudication or prospective confirmation of bleeding events and due to its use of a propensity score weighting to control for the probability of using dabigatran or warfarin.[17] On the other hand, another meta-analysis, performed in patients treated for acute venous thromboembolism only, showed a non-significant 22% reduction in gastrointestinal bleeding across all DOACs.[20] A recent real-world retrospective cohort study, however, did not show a difference in AF and non-AF users between dabigatran and warfarin, nor between rivaroxaban and warfarin, in the risk of gastrointestinal bleeding. However, in two population-based studies, there did seem to be a difference in gastrointestinal bleeding between older AF and non-AF patients using dabigatran (>76 years and ≥80 years, respectively),[21 22] with a higher risk of bleeding in the elderly, particularly in older women.[23]

For all-cause mortality, we show moderate evidence of an interaction for both doses of dabigatran compared with warfarin, with a mortality reduction in younger patients and loss of this benefit with advanced age. The p values for interaction are significant, and in the STEPP figure (figure 5), the warfarin and dabigatran curves are separate at younger ages but converge at about age 80, where death rates between both dabigatran doses and warfarin are comparable. The mortality benefit of dabigatran at younger ages is likely related to having reduction in stroke together with reduction in both intracranial and extracranial bleeding. One hypothesis why this highly favourable confluence of effects is less pronounced with increasing age could be the age–treatment interaction related to extracranial bleeding for both doses of dabigatran.

One might suspect that the underlying mechanism of the age–treatment interaction related to extracranial major bleeding is at least, in part, related to increased exposure to dabigatran in the elderly, caused by age-related decline in renal function. Dabigatran is mostly cleared by the kidneys, and dabigatran plasma concentration increases with decreasing creatinine clearance. However, our data indicate that the age–treatment interaction for extracranial major bleeding is also significant in elderly patients (aged ≥80 years) with adequate renal function (estimated glomerular filtration rate ≥60 ml/min; see online appendix table 1). Indeed, the kidneys decline in the elderly, but there may also be changes in several other organs due to frequent comorbidities and various comedications, leading to an increased risk of both thromboembolic and bleeding events. In fact, a recent paper suggested that, in addition to renal failure, comorbidities such as heart failure, previous *Helicobacter pylori* infection, alcohol abuse and comedications such as antiplatelet therapy and digoxin use also increase the risk of extracranial bleeding, specifically gastrointestinal bleeding.[24] In our study, patients with age ≥85 years indeed had a higher mean $CHADS_2$ score, but the aforementioned comorbidities (if available) were not more common in the oldest age group in our analysis, except for poorer renal function.

Intracranial and extracranial bleeding would both be expected to increase with increasing dabigatran plasma concentration, related to age-related decline in renal function, which is not the case. We have, however, observed that the treatment effects of dabigatran (compared with warfarin) vary with decreasing renal function, and this affects intracranial and extracranial bleeding in a way that is similar to the way it is affected by changing age. There was no significant interaction between creatinine clearance (calculated according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) estimate) and the effects of dabigatran 150 mg twice daily on stroke or non-CNS systemic embolism

or intracranial bleeding.[25] The benefit of dabigatran 150 mg twice daily for the reduction of stroke or intracranial bleeding was highly consistent across the range of renal functions studied. However, there were significant interactions between declining kidney function and major bleeding, similar to those reported with increasing age in the present paper. As age and kidney function are highly correlated due to the incorporation of age in the Cockcroft-Gault calculation, it is not possible with the present data to determine primary causality. For the very elderly, aged ≥85 years at baseline, results need to be interpreted with caution, as only 4% of patients fell into this category, of which only 79 subjects (0.4%) were aged 90 years or above.

A previous RE-LY analysis has shown that ischaemic stroke and bleeding outcomes are correlated with dabigatran plasma concentrations, with dabigatran levels being highly dependent on renal function and age.[26] However, no literature is available yet on whether adjustment of dabigatran dosing to measured plasma concentrations leads to decreased stroke or bleeding outcomes in patients with high levels, nor for which level of dabigatran plasma concentrations should be aimed in the elderly population; therefore, it is too early to advocate for adaptation to measured dabigatran plasma levels.

The clinical implications of the present analyses are of interest. Both doses of dabigatran provide excellent protection against stroke and non-CNS systemic embolism and much lower rates of intracranial bleeding than warfarin, irrespective of age. The interaction between age and treatment for extracranial major bleeding appears to be clinically significant but can be mitigated by reducing the dabigatran dose in elderly patients from dabigatran 150 mg twice daily to 110 mg twice daily. The data of the present analysis support the European Union[27] and Canadian approaches (and those of many countries) to dabigatran dose selection, which recommends dabigatran 110 mg twice daily for elderly patients (80 years of age and over).

Key messages

What is already known on this subject?
The prevalence of atrial fibrillation (AF) increases with advancing age, as well as the absolute risk of stroke with AF. Vitamin K antagonists reduce stroke risk in AF patients. The RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial demonstrated the superiority of dabigatran 150 mg twice daily and the non-inferiority of 110 mg twice daily compared with warfarin for stroke prevention in AF. Both doses of dabigatran also reduced intracranial bleeding.

What might this study add?
This study shows that both doses of dabigatran provide highly consistent protection against stroke and systemic embolism and much lower rates of intracranial bleeding compared with warfarin across all ages and age groups. This study also shows a seemingly important interaction between age and treatment for extracranial bleeding for dabigatran; there is a strong advantage of both doses of dabigatran compared with warfarin in younger patients, which diminishes with increasing age and which, for the higher dabigatran dose, eventually reverses for patients in the eighth decade.

How might this impact on clinical practice?
The interaction between age and treatment for extracranial major bleeding appears to be clinically significant but can be mitigated by reducing the dabigatran dose in elderly patients (80 years of age and older) from dabigatran 150 mg twice daily to 110 mg twice daily.

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IMAGE CHALLENGE

A middle-aged woman with a heavy heart

CLINICAL INTRODUCTION

A 51-year-old woman was referred to our hospital with a 4-month history of progressive dyspnoea on exertion (New York Heart Association Functional Classification III), chest heaviness, dry cough, weight loss and tiredness. She worked as cleaning woman and had no relevant medical history, apart from an Epstein-Barr Virus (EBV) infection 2 months before symptom onset. She did not smoke and family history was negative.

On examination, blood pressure was 104/80 mm Hg and heart rate was regular at 145 bpm. On auscultation, heart sounds were distant, muffled and there was no murmur. Minimal, bilateral pitting oedema was observed. Laboratory findings were unremarkable. During hospitalisation, cardiac monitoring revealed paroxysmal new-onset atrial fibrillation.

Chest radiography from a previous hospital had revealed cardiomegaly and subsequent echocardiography had shown pericardial effusion with diastolic dysfunction, for which she had received percutaneous pericardiocentesis. However, repeated echocardiography at our hospital showed recurrence of pericardial effusion with diastolic dysfunction and the presence of a pericardial mass. CT and Fluorine-18-fluorodeoxyglucose PET (^{18}F-FDG PET) scanning were done (figure 1).

QUESTION

Which of the following is the most likely diagnosis?
And based on patient history and imaging, are further diagnostics needed?

A. Benign pericardial lipoma
B. Fibrinofibrous pericarditis following EBV infection
C. Inflammatory pseudotumor
D. Primary cardiac lymphoma
E. Primary malignant pericardial mesothelioma

For the answer see page 1053

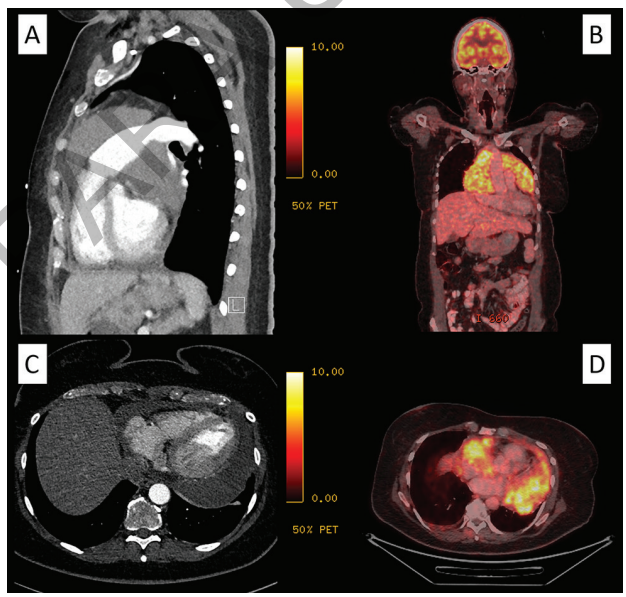

Figure 1 | Contrast-enhanced CT scanning and ^{18}F-FDG PET scanning. (A) CT scan, sagittal view; (B) ^{18}F-FDG PET scan, frontal view; (C) CT scan, axial view and (D) ^{18}F-FDG PET scan, axial view.