Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial

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Summary

Background **Effectiveness and safety of warfarin is associated with the time in therapeutic range (TTR) with an international normalised ratio (INR) of 2·0–3·0. In the Randomised Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, dabigatran versus warfarin reduced both stroke and haemorrhage. We aimed to investigate the primary and secondary outcomes of the RE-LY trial in relation to each centre's mean TTR (cTTR) in the warfarin population.**

Methods **In the RE-LY trial, 18 113 patients at 951 sites were randomly assigned to 110 mg or 150 mg dabigatran twice daily versus warfarin dose adjusted to INR 2·0–3·0. Median follow-up was 2·0 years. For 18 024 patients at 906 sites, the cTTR was estimated by averaging TTR for individual warfarin-treated patients calculated by the Rosendaal method. We compared the outcomes of RE-LY across the three treatment groups within four groups defined by the quartiles of cTTR. RE-LY is registered with ClinicalTrials.gov, number NCT00262600.**

Findings **The quartiles of cTTR for patients in the warfarin group were: less than 57·1%, 57·1–65·5%, 65·5–72·6%, and greater than 72·6%. There were no significant interactions between cTTR and prevention of stroke and systemic embolism with either 110 mg dabigatran (interaction p=0·89) or 150 mg dabigatran (interaction p=0·20) versus warfarin. Neither were any significant interactions recorded with cTTR with regards to intracranial bleeding with 110 mg dabigatran (interaction p=0·71) or 150 mg dabigatran (interaction p=0·89) versus warfarin. There was a significant interaction between cTTR and major bleeding when comparing 150 mg dabigatran with warfarin (interaction p=0·03), with less bleeding events at lower cTTR but similar events at higher cTTR, whereas rates of major bleeding were lower with 110 mg dabigatran than with warfarin irrespective of cTTR. There were significant interactions between cTTR and effects of both 110 mg and 150 mg dabigatran versus warfarin on the composite of all cardiovascular events (interaction p=0·036 and p=0·0006, respectively) and total mortality (interaction p=0·066 and p=0·052, respectively) with reduced event rates at low cTTR, and similar rates at high cTTR.**

Interpretation **The benefits of 150 mg dabigatran at reducing stroke, 110 mg dabigatran at reducing bleeding, and both doses at reducing intracranial bleeding versus warfarin were consistent irrespective of centres' quality of INR control. For all vascular events, non-haemorrhagic events, and mortality, advantages of dabigatran were greater at sites with poor INR control than at those with good INR control. Overall, these results show that local standards of care affect the benefits of use of new treatment alternatives.**

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Introduction

Vitamin K antagonists, such as warfarin, can reduce risk of stroke in patients with atrial fibrillation, but the benefits are seen only over a narrow therapeutic range. Treatment with vitamin K antagonists needs regular laboratory-guided adjustments of the dose because response to treatment is affected by interactions with food and drugs.[1–3] The lowest risk of stroke and bleeding is reached by maximising the time in the optimum therapeutic range (TTR), with an international normalised ratio (INR) of 2·0–3·0.[4–9] However, there are large variations in TTR between individuals, sites, and countries, all of which affect patient outcomes.[10–12]

Dabigatran etexilate is an oral direct thrombin inhibitor that provides stable anticoagulation at a fixed dose without any need for laboratory control. In the Randomised Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial,[13] in patients who had atrial fibrillation and at least one additional risk factor for stroke 150 mg dabigatran twice daily reduced both stroke and intracranial and life-threatening bleeding without any significant change in overall major bleeding compared with warfarin, whereas 110 mg dabigatran twice daily was non-inferior at reducing risk of stroke, but reduced intracranial, life-threatening, and major bleeding.[14] The mean TTR of 64% in the warfarin group is similar to that in other prospective randomised trials[10,12] and a meta-analysis.[15] Although this

value might seem low, observational data from usual clinical practice often show even lower means.[11,16] Therefore, the overall standards of anticoagulation in the warfarin group of RE-LY correspond well to contemporary standards for such treatment. As in previous multicentre multinational trials of anticoagulation, there were wide variations in INR control between countries and sites, which have led to questions of the relevance of the overall findings for countries and sites with better mean INR control. We therefore did a prespecified assessment of the primary and secondary outcomes of the RE-LY trial in relation to the quality of INR control. In the absence of any indicator of anticoagulation status in the dabigatran groups, the average TTR each centre achieved in its patients treated with warfarin was used as an approximation of quality of INR control for all its patients (centre's mean TTR [cTTR]) receiving warfarin.[10] The objective was therefore to assess the effects of centre-based INR control on these outcomes.[13]

Methods

Patients

The detailed design and primary results of RE-LY have been published.[14] 18 113 patients were recruited from 951 clinical centres in 44 countries. Inclusion criteria were documented atrial fibrillation and at least one of the following: previous stroke or transient ischaemic attack; congestive heart failure or reduced left ventricular ejection fraction (<40%); at least 75 years of age; or at least 65 years of age with diabetes mellitus, hypertension, or coronary artery disease. Exclusion criteria included severe heart valve disorder, recent stroke, increased risk of haemorrhage, creatinine clearance less than 30 mL/min, or active liver disease.

The study was approved by all appropriate national regulatory authorities and ethics committees. All patients provided written informed consent before study entry.

Randomisation and masking

In RE-LY patients were randomly assigned (1:1:1) to 110 mg dabigatran, 150 mg dabigatran, or warfarin by an interactive, automated telephone system. Dabigatran was supplied in capsules containing either 110 mg or 150 mg. Warfarin was supplied in 1 mg, 3 mg, or 5 mg tablets and adjusted locally to achieve an INR of 2·0–3·0 on the basis of INR measurements that were obtained at least once per month. Investigators and patients were masked to dabigatran dose but not to warfarin dose.

Procedures

The primary efficacy outcome in the RE-LY trial was stroke or systemic embolism. The primary safety outcome was major haemorrhage. Secondary outcomes were stroke, systemic embolism, and death. Other outcomes were myocardial infarction, pulmonary embolism, and transient ischaemic attack. The primary net benefit–risk outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major haemorrhage. Patients were followed up 14 days after randomisation, at 1 and 3 months, every 3 months thereafter for the first year, and then every 4 months until the end of the study.

Stroke was defined as sudden onset of focal neurological deficit consistent with the territory of a major cerebral artery and categorised as ischaemic, haemorrhagic, or unspecified. Haemorrhagic transformation of ischaemic stroke was not deemed to be haemorrhagic stroke. Intracranial haemorrhage included haemorrhagic stroke and subdural or subarachnoid haemorrhage. Systemic embolism was an acute vascular occlusion of a limb or organ documented by imaging, surgery, or autopsy. Major bleeding was defined as a reduction in haemoglobin concentration by at least 20 g/L, transfusion of at least two units of blood, or symptomatic bleeding in a crucial area or organ. Life-threatening bleeding was a subset of major bleeding that included fatal bleeding; symptomatic intracranial bleeding; bleeding with a decrease in haemoglobin concentration of at least 50 g/L; or bleeding requiring transfusion of at least four units of blood, inotropic agents, or surgery. All other bleedings were regarded as minor. All primary

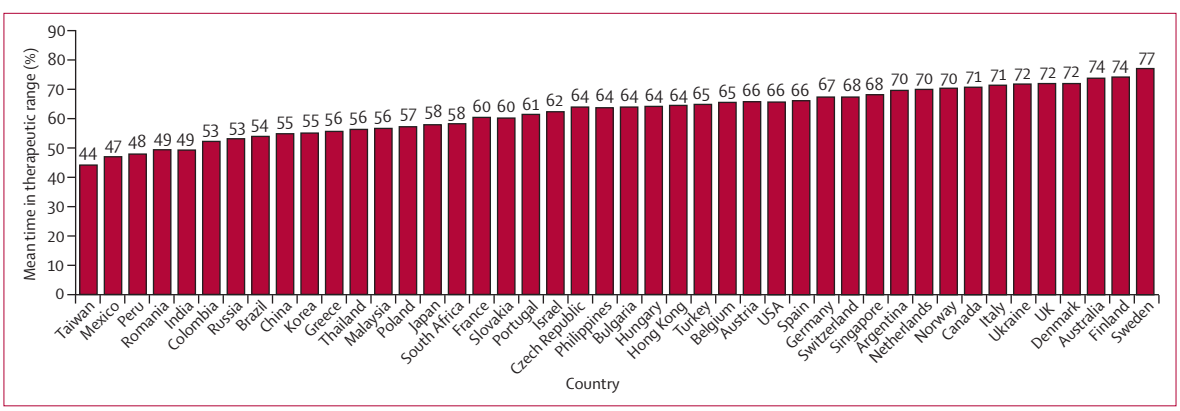

Figure 1: **Country distribution of mean time in therapeutic range in the RE-LY trial**

	cTTR				p value
	<57·1% (n=4510)	57·1–65·5% (n=4564)	65·5–72·6% (n=4445)	>72·6% (n=4505)	
Individual TTR in the warfarin population	50·7 (34·8–63·8)	63·0 (52·2–73·4)	70·3 (61·3–78·8)	78·9 (70·9–86·7)	..
Age (years)	70·0 (9·5)	71·3 (8·8)	72·1 (8·3)	72·5 (7·8)	<0·0001
Weight (kg)	77·3 (18·6)	82·9 (20·5)	85·7 (20·0)	84·9 (18·3)	<0·0001
Systolic blood pressure (mm Hg)	130·7 (17·6)	130·0 (17·0)	130·7 (17·5)	132·5 (17·7)	<0·0001
Diastolic blood pressure (mm Hg)	77·7 (10·3)	76·4 (10·6)	76·6 (10·6)	77·4 (10·5)	<0·0001
Men	2701 (60%)	2946 (65%)	2908 (65%)	2902 (64%)	0·0014
Atrial fibrillation type*					
Persistent	1718 (38%)	1331 (29%)	1441 (32%)	1266 (28%)	<0·0001
Paroxysmal	1355 (30%)	1590 (35%)	1447 (33%)	1514 (34%)	<0·0001
Permanent	1436 (32%)	1640 (36%)	1557 (35%)	1723 (38%)	<0·0001
CHADS2 score†	2·2 (1·1)	2·2 (1·1)	2·1 (1·1)	2·0 (1·1)	<0·0001
0–1	1262 (28%)	1457 (32%)	1426 (32%)	1593 (35%)	<0·0001
2	1658 (37%)	1593 (35%)	1556 (35%)	1624 (36%)	0·20
3–6	1590 (35%)	1514 (33%)	1463 (33%)	1287 (29%)	<0·0001
Previous stroke	693 (15%)	587 (13%)	524 (12%)	462 (10%)	<0·0001
Previous myocardial infarction	648 (14%)	775 (17%)	804 (18%)	762 (17%)	<0·0001
Heart failure	1725 (38%)	1523 (33%)	1298 (29%)	1216 (27%)	<0·0001
Diabetes mellitus	1079 (24%)	1111 (24%)	1059 (24%)	950 (21%)	0·0008
Hypertension	3561 (79%)	3597 (79%)	3546 (80%)	3508 (78%)	0·18
Baseline drugs					
Aspirin	1940 (43%)	1899 (42%)	1720 (39%)	1608 (36%)	<0·0001
Angiotensin receptor blocker	1109 (25%)	1055 (23%)	1031 (23%)	1111 (25%)	0·15
Angiotensin-converting enzyme inhibitors	1958 (43%)	1980 (43%)	2021 (45%)	2110 (47%)	0·0014
β blocker	2545 (56%)	2799 (61%)	2877 (65%)	3094 (69%)	<0·0001
Amiodarone	658 (15%)	505 (11%)	407 (9%)	352 (8%)	<0·0001
Statins	1647 (37%)	2039 (45%)	2177 (49%)	2136 (47%)	<0·0001
Proton-pump inhibitors	590 (13%)	591 (13%)	640 (14%)	662 (15%)	0·028
H2 blockers	188 (4%)	197 (4%)	197 (4%)	135 (3%)	0·0014

Data are median (IQR), mean (SD), or number (%). cTTR=centre's mean time in therapeutic range. TTR=time in therapeutic range. *cTTR <57·1% n=4509; cTTR 57·1–65·5% n=4561; cTTR >72·6% n=4503. †cTTR >72·6% n=4504.

Table 1: **Patient characteristics**

and secondary outcome events were adjudicated by two experts who were masked to treatment allocation.

Statistical analysis

During the whole trial we assessed the quality of warfarin treatment by calculating the individual TTR (iTTR) for individual patients by the Rosendaal method.[17] We excluded INRs during the first week of the study, during temporary or permanent discontinuation, and during the first week after treatment was restarted. The quality of INR control during the trial was reported back to each centre and we provided advice for optimum INR control and recommendations to use the study nomogram for optimum warfarin treatment. In this analysis we then calculated cTTRs for individual centres as an average of all iTTRs in the warfarin group in each centre. We assessed the distributions of and relations between cTTR and iTTR in the warfarin group and identified interquartile limits. The effects of patients' baseline characteristics, time in the trial, and cTTR on the variation of iTTR in the warfarin-treated patients were investigated in multivariate analyses.

The outcomes of RE-LY were compared across the three treatment groups within four groups defined by the quartiles of cTTR. The results are presented as hazard ratios and 95% CIs. Tests for interactions between cTTR, randomised treatment, and outcome events were assessed by multivariate backward stepwise Cox regression analyses with the following independent variables: interaction variable cTTR×randomised treatment strategy, randomised strategy, and individual cTTR. The following background characteristics were used as individual variables: age, sex, bodyweight, atrial fibrillation type, CHADS2 score,[1] previous stroke, previous myocardial infarction, heart failure, diabetes mellitus, hypertension, baseline drugs (aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, amiodarone, statins, proton-pump inhibitors, and H2 blockers), and previous

long-term treatment with vitamin K antagonists. The following outcome events were tested as the dependent factors in these analyses: stroke and systemic embolism; major bleeding; intracranial bleeding; death; the composite of stroke, systemic embolism, myocardial infarction, pulmonary embolism, death, and major bleeding; and the composite of non-haemorrhagic stroke, systemic embolism, myocardial infarction, pulmonary embolism, and death. All analyses were done separately for 110 mg dabigatran twice daily versus warfarin and for 150 mg dabigatran twice daily versus warfarin. There was no correction for multiple testing.

The RE-LY trial is registered with ClinicalTrials.gov, number NCT00262600.

Role of the funding source

The study was funded by Boehringer Ingelheim and coordinated by the Population Health Research Institute (Hamilton, ON, Canada), which independently managed the database and did the data analyses. An operations committee, with assistance from an international steering committee, was responsible for the study design, conduct, and reporting. The lead authors (LW, SYu, SJC) had full access to individual data and designed the statistical analysis. LW had final responsibility for the decision to submit for publication.

Results

18 024 patients from 906 sites were included in the investigations of relations to cTTR by applying cTTR as a proxy in all patients in each centre. The cTTR could not be estimated in 45 of the 951 participating sites because serial INR values were not available for any patients on warfarin maintenance treatment.

On the basis of observations in 5791 patients who were randomly assigned to receive warfarin, the quartiles of iTTR were: less than 53·6%, 53·6–67·2%, 67·2–78·4%, and more than 78·4%. In the warfarin cohort, there were significant associations between the iTTR quartiles and stroke and systemic embolism (2·34%, 1·72%, 1·42%, and 1·25%; p=0·0010), major bleeding (4·95%, 3·71%, 2·98%, and 2·65%; p<0·0001), total mortality (7·48%, 3·30%, 2·27%, and 2·65%; p<0·0001), and the composite of stroke, systemic embolism, pulmonary embolism, death, and major bleeding (12·32%, 7·35%, 5·55%, and 5·4%; p<0·0001). The quality of INR control also varied between different countries (figure 1). The quartiles of cTTR, which were based on the distribution of cTTR in the 906 sites, were less widely distributed than the iTTR quartiles: less than 57·1%, 57·1–65·5%, 65·5–72·6%, and more than 72·6%. In a univariate analysis with iTTR as the dependent variable, there was a modest correlation between iTTR and cTTR (r=0·588). In a multivariate analysis, the most important baseline characteristic associated with the variability in iTTR was cTTR (data not shown). Other factors contributing to improved iTTR were time in the study, previous use of warfarin, and male sex, whereas factors associated with poorer iTTR were smoking, heart failure, amiodarone use, and insulin treatment (data not shown). Several of these patient-related factors that determine iTTR might also have affected the response to dabigatran (eg, amiodarone use, time in study, and smoking), although not necessarily in the same direction; thus we only used the structural factor cTTR as the basis for the model when comparing the effect of INR control on outcomes.

When comparing the populations within the different cTTR quartiles there were several significant differences

	110 mg dabigatran			150 mg dabigatran			Warfarin			110 mg dabigatran *vs* warfarin		150 mg dabigatran *vs* warfarin	
	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	HR (95% CI)	p (interaction)	HR (95% CI)	p (interaction)
Stroke and systemic embolism													
<57·1%	1497	55	1·91	1509	32	1·10	1504	54	1·92	1·00 (0·68–1·45)	..	0·57 (0·37–0·88)	..
57·1–65·5%	1524	51	1·67	1526	32	1·04	1514	62	2·06	0·81 (0·56–1·17)	..	0·50 (0·33–0·77)	..
65·5–72·6%	1474	40	1·34	1484	31	1·04	1487	45	1·51	0·89 (0·58–1·36)	..	0·69 (0·44–1·09)	..
>72·6%	1482	36	1·23	1514	38	1·27	1509	40	1·34	0·92 (0·59–1·45)	0·89	0·95 (0·61–1·48)	0·20
Non-haemorrhagic stroke and systemic embolism													
<57·1%	1497	51	1·77	1509	26	0·89	1504	46	1·63	1·09 (0·73–1·62)	..	0·54 (0·34–0·88)	..
57·1–65·5%	1524	46	1·51	1526	30	0·98	1514	49	1·63	0·92 (0·62–1·38)	..	0·59 (0·38–0·94)	..
65·5–72·6%	1474	39	1·31	1484	30	1·01	1487	33	1·11	1·19 (0·75–1·89)	..	0·91 (0·56–1·50)	..
>72·6%	1482	32	1·10	1514	35	1·17	1509	29	0·97	1·13 (0·69–1·87)	0·86	1·21 (0·74–1·98)	0·076
Intracranial bleeding													
<57·1%	1497	8	0·28	1509	10	0·34	1504	18	0·64	0·43 (0·19–1·00)	..	0·53 (0·25–1·15)	..
57·1–65·5%	1524	9	0·30	1526	13	0·42	1514	28	0·93	0·31 (0·15–0·66)	..	0·45 (0·24–0·88)	..
65·5–72·6%	1474	4	0·13	1484	7	0·24	1487	20	0·67	0·20 (0·07–0·58)	..	0·35 (0·15–0·82)	..
>72·6%	1482	6	0·21	1514	9	0·30	1509	23	0·77	0·27 (0·11–0·66)	0·71	0·39 (0·18–0·84)	0·89

HR=hazard ratio.

Table 2: **Primary endpoint and its components according to centre's mean time in therapeutic range**

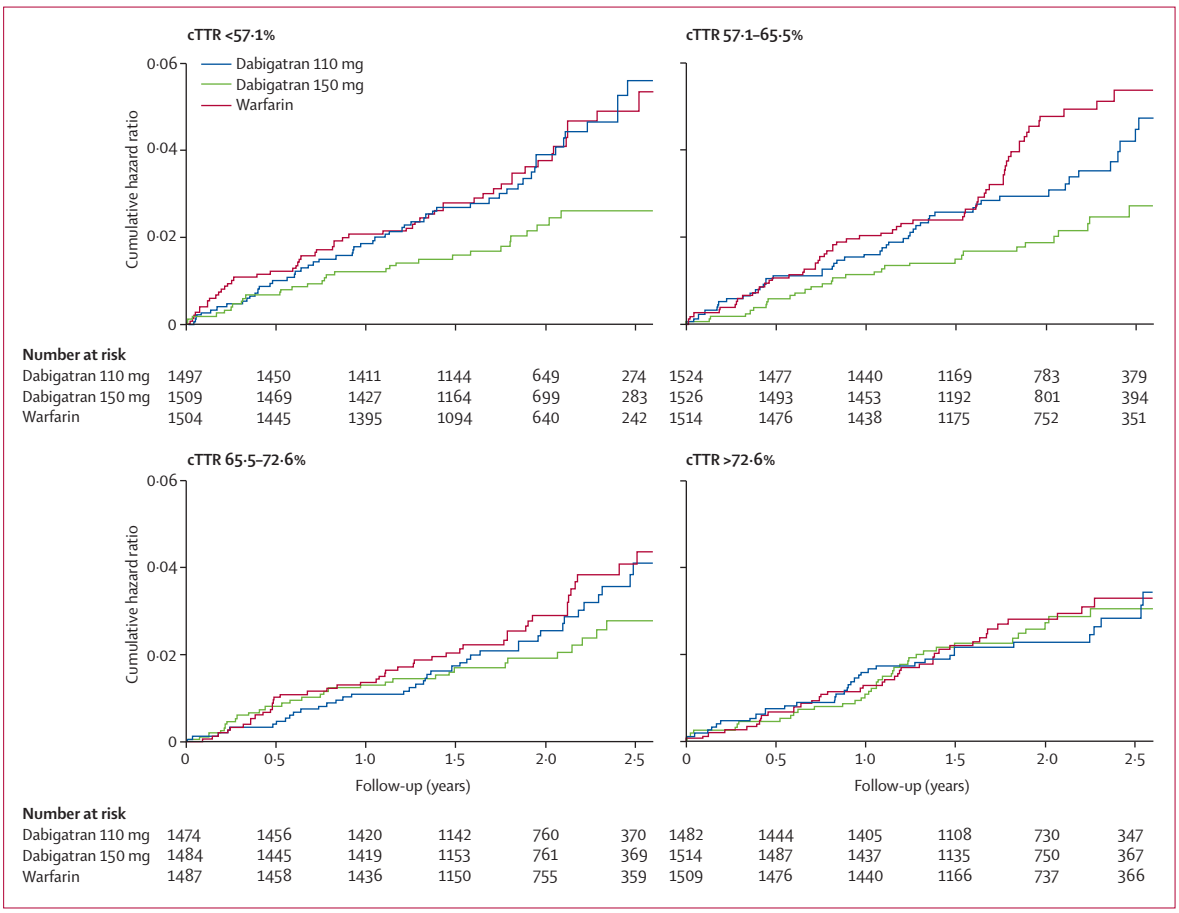

Figure 2: **Time to primary outcome in each quartile of centre's mean time in therapeutic range**
cTTR=centre's mean time in therapeutic range.

in baseline characteristics (table 1). However, because random allocation to the investigational treatment groups was stratified by centre, these were well balanced between the treatment groups within each of the cTTR quartiles.

In the total population, the rate of the primary outcome of stroke and systemic embolism was reduced from 1·71% per year (202/6022) on warfarin, to 1·54% per year (183/6015) on 110 mg dabigatran (non-inferiority p<0·001), to 1·11% per year (134/6076) on 150 mg dabigatran (superiority p<0·001). Event rates seemed to decrease with higher cTTR in the warfarin group. However, there were no significant interactions between cTTR and stroke and systemic embolism with either dose of dabigatran versus warfarin (table 2, figure 2). The rate of haemorrhagic stroke was 0·38% per year (45/6022) on warfarin versus 0·12% per year (14/6015) on 110 mg dabigatran (superiority p<0·001) and 0·10% per year (12/6076) on 150 mg dabigatran (superiority p<0·001). The rates of intracranial bleeding in the warfarin group were not associated with the cTTR and were consistently lower in both dabigatran groups than the warfarin group irrespective of cTTR (table 2). The rate of non-haemorrhagic stroke and systemic embolism seemed to be lower with higher cTTR in the warfarin group (interaction p=0·08).

In the total population, the rate of major bleeding was 3·57% per year (421/6022) on warfarin versus 2·87% per year (342/6015) on 110 mg dabigatran (superiority p=0·003) and 3·32% per year (399/6076) on 150 mg dabigatran (superiority p=0·31). The rate of major bleeding, as well as major gastrointestinal bleeding, was numerically lower at higher cTTR quartiles in the warfarin group. When comparing major bleedings between the 150 mg dose of dabigatran and warfarin, there were benefits at lower cTTR but similar results at higher cTTR (interaction p=0·03; table 3, figure 3). There was a higher rate of major gastrointestinal bleeding with 150 mg dabigatran than warfarin at higher cTTR (interaction p=0·019; table 3). Finally, there was an increase in total bleeding rate with increasing cTTR in all three treatment groups, without any significant interactions between the treatment groups (table 3, figure 3).

Mortality rates were 4·13% per year (487/6022) on warfarin versus 3·75% per year (446/6015) on 110 mg dabigatran (superiority p<0·13) and 3·64% per year

	110 mg dabigatran			150 mg dabigatran			Warfarin			110 mg dabigatran *vs* warfarin		150 mg dabigatran *vs* warfarin	
	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	HR (95% CI)	p (interaction)	HR (95% CI)	p (interaction)
Major bleeding													
<57·1%	1497	68	2·36	1509	74	2·54	1504	101	3·59	0·65 (0·48–0·89)	..	0·71 (0·52–0·96)	..
57·1–65·5%	1524	103	3·38	1526	102	3·33	1514	124	4·13	0·82 (0·63–1·06)	..	0·81 (0·62–1·05)	..
65·5–72·6%	1474	84	2·82	1484	113	3·80	1487	101	3·40	0·83 (0·62–1·11)	..	1·13 (0·87–1·48)	..
>72·6%	1482	82	2·81	1514	108	3·60	1509	93	3·11	0·90 (0·67–1·21)	0·50	1·16 (0·88–1·54)	0·03
Major gastrointestinal bleeding													
<57·1%	1497	33	1·15	1509	44	1·51	1504	40	1·42	0·81 (0·51–1·29)	..	1·08 (0·70–1·66)	..
57·1–65·5%	1524	51	1·67	1526	54	1·76	1514	48	1·60	1·05 (0·71–1·56)	..	1·11 (0·75–1·63)	..
65·5–72·6%	1474	40	1·34	1484	73	2·46	1487	33	1·11	1·22 (0·77–1·94)	..	2·26 (1·50–3·40)	..
>72·6%	1482	37	1·27	1514	52	1·73	1509	26	0·87	1·46 (0·89–2·41)	0·36	2·00 (1·25–3·21)	0·019
Total bleeding													
<57·1%	1497	351	12·20	1509	420	14·42	1504	466	16·56	0·71 (0·62–0·82)	..	0·89 (0·78–1·01)	..
57·1–65·5%	1524	428	14·04	1526	486	15·88	1514	570	18·96	0·71 (0·63–0·80)	..	0·82 (0·73–0·93)	..
65·5–72·6%	1474	479	16·07	1484	512	17·24	1487	557	18·74	0·85 (0·75–0·96)	..	0·92 (0·81–1·03)	..
>72·6%	1482	468	16·03	1514	542	18·08	1509	555	18·55	0·84 (0·74–0·95)	0·076	1·00 (0·89–1·12)	0·15

HR=hazard ratio.

Table 3: **Bleeding events according to centre's mean time in therapeutic range**

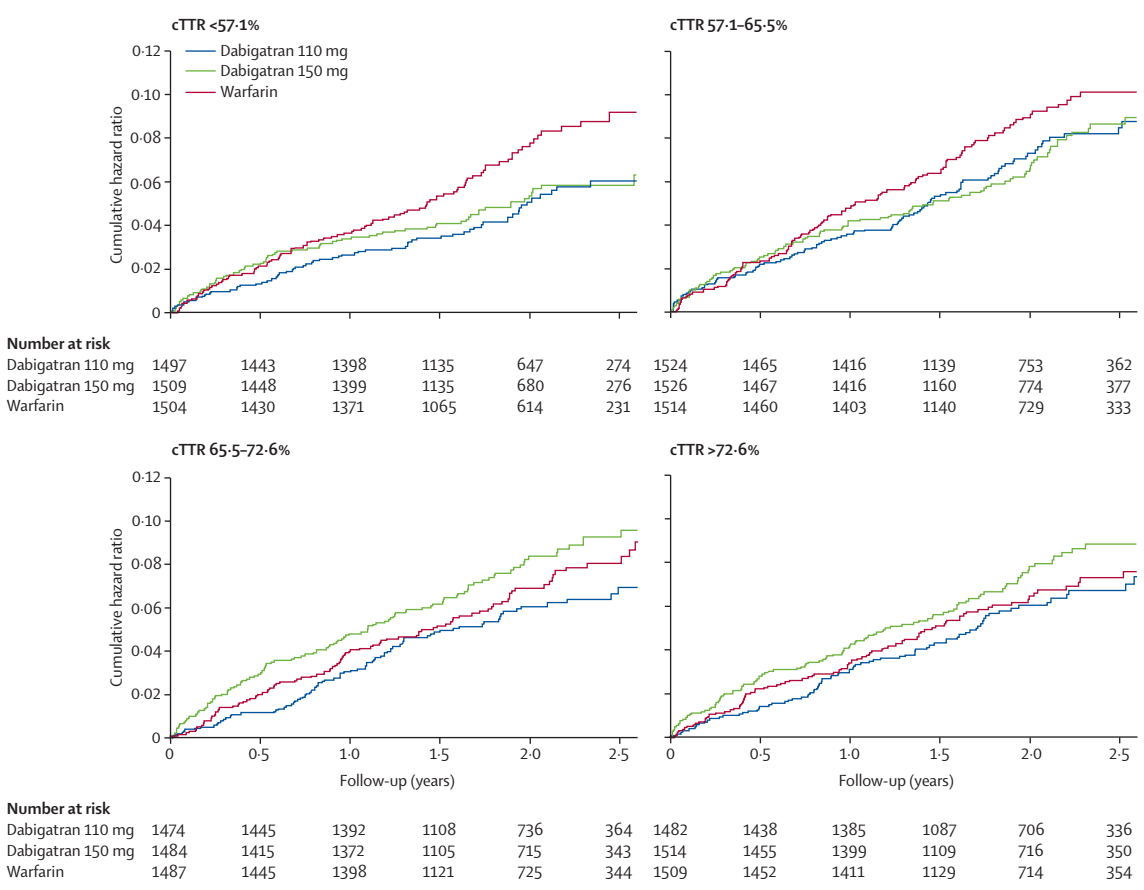

Figure 3: **Time to major bleeding event in each quartile of centre's mean time in therapeutic range**
cTTR=centre's mean time in therapeutic range.

	110 mg dabigatran			150 mg dabigatran			Warfarin			110 mg dabigatran *vs* warfarin		150 mg dabigatran *vs* warfarin	
	Patients (n)	Events	Rate per 100 person–years	Patients (n)	Events	Rate per 100 person–years	Patients (n)	Events	Rate per 100 person–years	HR (95% CI)	p (interaction)	HR (95% CI)	p (interaction)
Stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, and major bleeding													
<57·1%	1497	220	7·65	1509	199	6·83	1504	285	10·13	0·74 (0·62–0·89)	..	0·67 (0·56–0·80)	..
57·1–65·5%	1524	239	7·84	1526	217	7·09	1514	241	8·03	0·97 (0·81–1·16)	..	0·87 (0·73–1·05)	..
65·5–72·6%	1474	205	6·88	1484	220	7·41	1487	212	7·13	0·97 (0·80–1·17)	..	1·05 (0·87–1·27)	..
>72·6%	1482	200	6·85	1514	212	7·07	1509	192	6·42	1·07 (0·87–1·30)	0·036	1·11 (0·91–1·35)	0·0006
Stroke, systemic embolism, pulmonary embolism, myocardial infarction, and cardiovascular death													
< 57·1%	1497	150	5·21	1509	115	3·95	1504	175	6·22	0·83 (0·67–1·04)	..	0·64 (0·50–0·80)	..
57·1–65·5%	1524	131	4·30	1526	107	3·50	1514	130	4·33	0·99 (0·78–1·27)	..	0·80 (0·62–1·04)	..
65·5–72·6%	1474	111	3·72	1484	108	3·64	1487	115	3·87	0·97 (0·74–1·25)	..	0·94 (0·72–1·22)	..
>72·6%	1482	112	3·84	1514	108	3·60	1509	91	3·04	1·27 (0·97–1·67)	0·14	1·19 (0·90–1·57)	0·006
Non-haemorrhagic stroke, systemic embolism, pulmonary embolism, myocardial infarction, and cardiovascular death													
<57·1%	1497	170	5·91	1509	147	5·05	1504	210	7·46	0·79 (0·64–0·97)	..	0·67 (0·55–0·83)	..
57·1–65·5%	1524	170	5·58	1526	148	4·84	1514	153	5·10	1·09 (0·88–1·36)	..	0·94 (0·75–1·18)	..
65·5–72·6%	1474	147	4·93	1484	144	4·85	1487	138	4·74	1·04 (0·88–1·32)	..	1·03 (0·81–1·29)	..
>72·6%	1482	146	5·00	1514	137	4·57	1509	115	3·91	1·29 (1·01–1·64)	0·017	1·17 (0·91–1·50)	0·0046
Total death													
<57·1%	1497	120	4·17	1509	112	3·85	1504	161	5·72	0·73 (0·58–0·92)	..	0·67 (0·53–0·85)	..
57·1–65·5%	1524	121	3·97	1526	115	3·75	1514	123	4·09	0·97 (0·75–1·24)	..	0·92 (0·71–1·18)	..
65·5–72·6%	1474	95	3·19	1484	108	3·64	1487	110	3·70	0·86 (0·65–1·13)	..	0·98 (0·75–1·28)	..
>72·6%	1482	105	3·60	1514	99	3·30	1509	91	3·04	1·18 (0·89–1·57)	0·066	1·08 (0·81–1·44)	0·052

HR=hazard ratio.

Table 4: **Composite cardiovascular events and total mortality according to centres' mean time in therapeutic range**

(438/6076) on 150 mg dabigatran (superiority p<0·051). Total mortality was lower at higher cTTR in the warfarin group (table 4); the interaction p value was 0·052 for the interaction between cTTR and the effects of 110 mg dabigatran and 0·066 for the effects of 150 mg dabigatran, with differences in mortality at lower cTTR but similar rates at higher cTTR. For all cardiovascular events, including total mortality and major bleeding, there were significantly lower event rates at higher cTTR in the warfarin group. There was a significant interaction between cTTR and the composite of all cardiovascular events when comparing 150 mg dabigatran versus warfarin (p=0·0006) and with 110 mg dabigatran versus warfarin (p=0·036). These interactions were mainly attributable to significant differences between groups in the rates of non-haemorrhagic events (interaction p=0·017 for 110 mg dabigatran *vs* warfarin; and interaction p=0·0046 for 150 mg dabigatran *vs* warfarin), with advantages at lower cTTR, whereas rates were greater at higher cTTR (table 4).

Discussion

In this analysis of the RE-LY trial we have shown fewer ischaemic strokes but not fewer occurrences of intracranial bleeding with increasing cTTR in the warfarin group. Accordingly, there were no significant interactions between cTTR control and total stroke with either dose of dabigatran compared with warfarin. Thus, these findings support the superiority of 150 mg dabigatran twice daily and the non-inferiority of 110 mg dabigatran twice daily versus warfarin for protection against stroke in atrial fibrillation irrespective of the quality of INR control that a centre can achieve. However, there seemed to be lower rates of non-haemorrhagic stroke at higher cTTR quartiles in the warfarin group, which is in accordance with previous findings.[4–9,12,18,19] Accordingly, 150 mg dabigatran was not superior to warfarin at reducing the risk of non-haemorrhagic stroke at higher cTTR quartiles.

We noted lower rates of total bleeding at sites with a lower cTTR in all three groups of the trial. These rates might be low because of underdosing or poor compliance at sites with lower cTTR or more thorough recording of bleedings at sites with better cTTR. In the warfarin group, but not in the dabigatran groups, there was a lower risk of both total major and gastrointestinal major bleeding at sites with better INR control, which is in accordance with other studies.[10,12] These lower risks led to significant interactions between cTTR and the risk of total and gastrointestinal major bleeding with 150 mg dabigatran but not 110 mg dabigatran versus warfarin. These findings support the lower bleeding risk of 110 mg dabigatran compared with warfarin irrespective of the centres' quality of INR control and a lower bleeding risk of the higher dabigatran dose at sites with with poor INR control. Intracranial bleeds were consistently lower with both doses of dabigatran than with warfarin irrespective of cTTR.

Mortality decreased with increasing cTTR in the warfarin group in accordance with previous reports,[4,6,18,19] which

resulted in significant interactions between cTTR and total mortality for both doses of dabigatran versus warfarin, with reductions at poorer but not at better INR control. Similarly, the reduction in the composite of mortality and non-haemorrhagic cardiovascular events, and the net clinical benefit with dabigatran versus warfarin was mainly seen at centres with poorer INR control. These findings are consistent with the results of a previous trial[10] in which the benefits of warfarin over aspirin plus clopidogrel were observed only at TTR greater than 65%. The absence of a significant interaction between cTTR and haemorrhagic stroke rates suggests that the effect of INR control on overall event rates is mainly driven by interactions between INR and non-haemorrhagic events, which is consistent with previous findings with warfarin.[4,7,8]

This study has several limitations. The analyses were prespecified for the primary outcome events but not for the secondary endpoints, which should therefore be deemed exploratory. The use of cTTR in the warfarin group as a proxy for INR control, both in the warfarin-treated patients and dabigatran-treated patients, has some limitations. cTTR might not appropriately represent INR control of individual patients and might not represent the full effect of INR control on outcome. Also, cTTR does not show the effect of good and poor treatment response, treatment adherence to dabigatran, or the effect of treatment discontinuations. Finally, cTTR is a post-randomisation variable and thus is also probably a marker of differences in overall care between centres, which might not be fully compensated for in the multivariate analyses. Furthermore, there was no correction of significance levels for multiple testing. Therefore, these analyses might mainly emphasise the importance of INR control for outcome events in patients treated with warfarin. However, in the absence of a common estimate of anticoagulation in all treatment groups, the present method of using the centres' mean INR seems to provide a good estimate of the benefits and risk of dabigatran compared with warfarin at different levels of INR control, especially because randomisation was stratified by centre, which reduces concerns about differences in patients' baseline characteristics between centres.

When assessing the outcomes in the RE-LY trial in relation to centre-based mean INR control, the primary efficacy results remained consistent, with reductions in the rates of stroke and intracranial bleeding with 150 mg dabigatran twice daily and similar reductions of stroke and major and intracranial bleeding with 110 mg dabigatran twice daily, irrespective of INR control. For major bleeding there was also a benefit with the 150 mg dose at sites with poor INR control. For secondary outcomes, such as non-haemorrhagic events and mortality, advantages of dabigatran were reported for sites with poorer INR control, whereas results were comparable in centres with better INR control. Overall, these results show that local standards of care affect the benefits of use of new treatment alternatives.

Contributors

LW, SYu, MDE, PAR, and SJC designed, led, and contributed equally to the running, statistical analyses, interpretation, and reporting of the results of the main RE-LY trial. MA, MF, MGF, PP, ALD, and JO participated in data collection in the main trial as national coordinators. This study was designed and lead by LW, SYu, and SJC. The statistical analyses were done by SYa. All co-authors participated in the interpretation of the results. LW drafted the first version of the manuscript and all subsequent versions thereafter. All co-authors critically reviewed all versions of the report and participated in the decision to submit the paper.

Conflicts of interest

LW has received consulting and lecture fees, honoraria, and research grants from Boehringer Ingelheim; research grants from AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, and Schering-Plough; honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Schering-Plough; consultant fees from Athera Biotechnologies, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Regado Biotechnologies; and lecture fees from AstraZeneca and Eli Lilly. SYu has received consulting fees, honoraria, and travel and grant support from Boehringer Ingelheim; and consulting fees from AstraZeneca, Bristol-Myers Squibb, and Sanofi-Aventis. MDE has received consulting fees and grant support from Boehringer Ingelheim, ARYx Therapeutics, Daiichi Sankyo, and Portola Pharmaceuticals; and consulting fees from Sanofi-Aventis, Pfizer, Bristol-Meyers Squibb, AstraZeneca, and Medtronic. MA has received consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, MSD, and Sanofi-Aventis; lecture fees from Boehringer Ingelheim; and a non-personal research grant from Boston Scientific. MF has received research grant and travel support from Boehringer Ingelheim. MGF has received travel support from AstraZeneca, Boehringer Ingelheim, Pfizer, Sanofi-Aventis, SPA, and Sigma Tau; lecture fees from AstraZeneca and Boehringer Ingelheim; and non-personal research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Sanofi-Aventis, Pfizer, SPA, Sigma Tau, and Takeda. PP has received consulting fees and travel support from Boehringer Ingelheim. AD has received consulting fees, honoraria, and travel support from Boehringer Ingelheim. JE has been an advisory board member for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Sanofi-Aventis; has received consulting fees, honoraria, and travel and grant support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Sanofi-Aventis; and has received honoraria from Corgenix Medical Corporation, Daiichi-Sankyo Eisai Pharmaceuticals, Eli Lilly, and McNeil. JO has been an advisory board member and has received lecture fees and travel and grant support from Boehringer Ingelheim; and has received lecture fees from AstraZeneca. PAR is an employee of Boehringer Ingelheim. SJC has received consulting fees and grant and travel support from Boehringer Ingelheim. No other potential conflict of interest relevant to this article was reported.

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