Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

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ABSTRACT

OBJECTIVE

To study the effectiveness and safety of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) dabigatran, rivaroxaban, and apixaban compared with warfarin in anticoagulant naïve patients with atrial fibrillation.

DESIGN

Observational nationwide cohort study.

SETTING

Three Danish nationwide databases, August 2011 to October 2015.

PARTICIPANTS

61678 patients with non-valvular atrial fibrillation who were naïve to oral anticoagulants and had no previous indication for valvular atrial fibrillation or venous thromboembolism. The study population was distributed according to treatment type: warfarin (n=35436, 57%), dabigatran 150 mg (n=12701, 21%), rivaroxaban 20 mg (n=7192, 12%), and apixaban 5 mg (n=6349, 10%).

MAIN OUTCOME MEASURES

Ischaemic stroke, death, any bleeding, and major bleeding.

RESULTS

Ischaemic stroke occurred annually in 1.5% of patients treated with warfarin: hazard ratio 0.83 (95% confidence interval 0.69 to 0.99). The hazard ratios for dabigatran and apixaban (2.8% and 4.9% annually, respectively) were non-significant compared with warfarin. The annual risk of death was significantly lower with apixaban (5.2%) and dabigatran (2.7%) (0.65, 0.56 to 0.75 and 0.63, 0.48 to 0.82, respectively) compared with warfarin (8.5%), but not with rivaroxaban (7.7%). For the combined endpoint of any bleeding, annual rates for apixaban (3.3%) and dabigatran (2.4%) were significantly lower than for warfarin (5.0%) (0.62, 0.51 to 0.74). Warfarin and rivaroxaban had comparable annual bleeding rates (5.3%).

CONCLUSION

All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting. No significant difference was found between NOACs and warfarin for ischaemic stroke. The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The use of non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) has been increasing since their introduction

Based on data from clinical practice, however, limited evidence exists on effectiveness and safety of NOACs compared with warfarin

WHAT THIS STUDY ADDS

No significant difference in risk of ischaemic stroke was evident between NOACs and warfarin

Rivaroxaban was associated with a lower risk of ischaemic stroke or systemic embolism than warfarin, but with comparable major bleeding rates

Dabigatran and apixaban had non-significant hazard ratios compared with warfarin for ischaemic stroke or systemic embolism, whereas major bleeding rates were significantly lower with reference to warfarin

Table 2 | Number of events, and crude and weighted event rates according to initiated treatment

Variables	Apixaban			Dabigatran			Rivaroxaban			Warfarin		
	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†
One year follow-up:												
Ischaemic stroke or systemic embolism	210	4.86	3.92	327	2.77	3.73	161	3.04	2.89	1004	3.28	3.25
Ischaemic stroke	204	4.71	3.72	321	2.72	3.68	156	2.95	2.79	920	3.00	3.01
All cause mortality	232	5.23	5.01	319	2.66	4.62	413	7.69	7.02	2652	8.52	7.41
Ischaemic stroke, systemic embolism, or death	424	9.81	8.71	623	5.28	7.92	537	10.15	9.38	3483	11.39	10.28
Any bleeding	121	3.78	3.13	253	2.77	2.85	186	5.57	4.83	959	5.53	4.71
Major bleeding	90	2.80	2.29	203	2.22	2.04	149	4.44	3.92	725	4.16	3.58
Intracranial bleeding	15	0.46	0.40	19	0.21	0.22	14	0.41	0.31	118	0.66	0.55
2.5 years' follow-up:												
Ischaemic stroke or systemic embolism	225	4.08	3.32	441	1.84	2.32	201	2.34	2.21	1447	2.39	2.33
Ischaemic stroke	219	3.97	3.17	427	1.78	2.26	196	2.28	2.15	1337	2.20	2.17
All cause mortality	274	4.82	4.69	600	2.44	4.04	592	6.74	6.31	4469	7.17	6.20
Ischaemic stroke, systemic embolism, or death	473	8.58	7.75	992	4.13	6.10	733	8.53	8.03	5524	9.11	8.13
Any bleeding	143	3.52	2.90	461	2.48	2.67	252	4.60	4.09	1579	4.60	3.93
Major bleeding	109	2.67	2.15	376	2.01	2.02	200	3.63	3.27	1198	3.46	2.98
Intracranial bleeding	18	0.43	0.41	35	0.18	0.17	23	0.40	0.31	190	0.53	0.44

*Events divided by 100 person years.

†Inverse probability of treatment weighted and expressed as population average treatment rates per 100 years.

Table 1 | Participant characteristics according to treatment. Values are numbers (percentages) unless stated otherwise

Characteristics	NOAC			Warfarin	All	Maximum standardised difference*	
	Apixaban	Dabigatran	Rivaroxaban			Before	After
No in group				35436	61678	-	-
Women	39.7 (2522)	33.9 (4304)	43.1 (3100)	41.2 (14598)	39.8 (24524)	0.19	0.02
Median (interquartile range) age (years)	71.3 (65.8-77.2)	67.6 (62.0-72.4)	71.8 (65.7-78.9)	72.4 (64.7-79.8)	70.9 (64.3-77.7)	0.45	0.02
Age >65	78.2 (4967)	64.4 (8180)	77.7 (5590)	74.2 (26295)	73.0 (45032)	0.31	0.02
Age >75	33.7 (2140)	13.9 (1766)	38.1 (2737)	41.4 (14655)	34.5 (21298)	0.58	0.03
Previous atrial fibrillation diagnose	68.9 (4374)	70.0 (8889)	60.2 (4333)	51.5 (18243)	58.1 (35839)	0.38	0.02
Mean (SD) CHA_2DS_2VASc score†	2.8 (1.6)	2.2 (1.4)	2.8 (1.6)	2.8 (1.7)	2.7 (1.6)	0.39	0.02
Mean (SD) HAS-BLED score‡	2.3 (1.2)	2.0 (1.1)	2.2 (1.2)	2.2 (1.2)	2.2 (1.2)	0.25	0.01
Cancer	16.1 (1021)	11.8 (1495)	16.1 (1159)	16.5 (5862)	15.5 (9537)	0.13	0.02
Ischaemic stroke, or systemic embolism, or TIA	21.1 (1339)	13.2 (1674)	16.8 (1209)	14.8 (5241)	15.3 (9463)	0.22	0.03
Heart failure or LVD	15.9 (1009)	9.3 (1187)	12.6 (908)	10.4 (3699)	11.0 (6803)	0.13	0.03
Vascular disease	13.9 (882)	10.4 (1319)	12.2 (879)	18.1 (6407)	15.4 (9487)	0.21	0.02
Renal dysfunction	2.4 (155)	1.1 (145)	1.8 (131)	6.6 (2346)	4.5 (2777)	0.26	0.04
COPD	8.9 (564)	6.2 (787)	8.8 (636)	9.6 (3403)	8.7 (5390)	0.12	0.02
Previous bleeding	14.0 (886)	9.9 (1257)	12.8 (923)	11.8 (4185)	11.8 (7251)	0.13	0.02
Hypertension	48.8 (3099)	47.0 (5971)	48.6 (3492)	50.6 (17932)	49.4 (30494)	0.07	0.01
Diabetes	15.8 (1000)	13.8 (1754)	14.0 (1006)	15.6 (5513)	15.0 (9273)	0.05	0.03
Aspirin	37.8 (2400)	38.2 (4853)	38.3 (2751)	42.0 (14895)	40.4 (24899)	0.09	0.01
β blocker	38.6 (2450)	40.1 (5093)	38.9 (2801)	41.0 (14518)	40.3 (24862)	0.05	0.01
NSAIDs	22.4 (1422)	24.5 (3114)	22.1 (1586)	24.3 (8616)	23.9 (14738)	0.06	0.01
Statins	40.6 (2577)	37.8 (4805)	38.4 (2764)	40.0 (14181)	39.4 (24327)	0.06	0.02

TIA=transient ischaemic attack; LVD=left ventricular dysfunction; COPD=chronic obstructive pulmonary disease; NSAIDs=non-steroidal anti-inflammatory drugs.

*Maximum standardised pairwise difference, before and after inverse probability of treatment weighting.

†Scores range from 0-9, reflecting risk of stroke in patients with atrial fibrillation not receiving anticoagulants (see supplementary table 2).

‡Scores range from 0-9, reflecting risk of bleeding in patients with atrial fibrillation receiving anticoagulants (see supplementary table 2).

ment compared with any of the alternatives. The likelihood of apixaban use (contrasted to the three other alternatives) was increased (odds ratio >1.1) in the presence of previous ischaemic stroke, systemic embolism, or transient ischaemic attack; vascular disease; bleeding; and hospital confirmed atrial fibrillation, but it was reduced (odds ratio <0.9) by renal impairment and aspirin use. Choice of dabigatran was increased with a hospital diagnosis of atrial fibrillation but reduced if the patient was female, and had vascular disease, renal impairment, chronic obstructive pulmonary disease (COPD), heart failure, or cancer. The probability for selecting rivaroxaban was increased by female sex, previous ischaemic stroke, systemic embolism, or transient ischaemic attack, or bleeding but reduced by vascular disease, renal impairment, heart failure, or use of non-steroidal anti-inflammatory drugs. Treatment with warfarin was more likely if the patient was female, had vascular disease, hypertension, renal impairment, COPD, heart failure, or cancer, or used aspirin but less likely in patients with a confirmed hospital diagnosis of atrial fibrillation.

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Regular Article

Improvement of anticoagulant treatment using a dynamic decision support algorithm
A Danish Cohort study

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ABSTRACT

Introduction: Warfarin is the most widely prescribed vitamin K antagonist and in the United States and Europe more than 10 million people are currently in long-term oral anticoagulant treatment. This study aims to retrospectively validate a dynamic statistical model providing dosage suggestions to patients in warfarin treatment.

Materials and methods: The model was validated on a cohort of 553 patients with a mean TTR of 83%. Patients in the cohort were self-monitoring and managed by a highly specialised anticoagulation clinic. The predictive model essentially consists of three parts handling INR history, warfarin dosage and biological noise, which allows for prediction of future INR values and optimal warfarin dose to stay on INR target. Further, the model is based on parameters initially being set to population values and gradually individualised during monitoring of patients.

Primary outcome: Time in therapeutic range was used as surrogate quality measure of the treatment, and model-suggested dosage of warfarin was used to assess the accuracy of the model performance.

Results: The accuracy of the model predictions measured as median absolute error was 0.53 mg/day (interquartile range from 0.25 to 1.0). The model performance was evaluated by the difference between observed and predicted warfarin intake in the preceding week of an INR measurement. In more than 70% of the cases where INR measurements were outside the therapeutic range, the model suggested a more reasonable dose than the observed intake.

Conclusion: Applying the proposed dosing algorithm can potentially further increase the time in INR target range beyond 83%.

Dabigatran Versus Warfarin for Atrial Fibrillation in Real-World Clinical Practice

A Systematic Review and Meta-Analysis

Robert J. Romanelli, PhD, MPH; Laura Nolting, BS; Marina Dolginsky, BS; Eunice Kym, PharmD; Kathleen B. Orrico, PharmD

Background—Trial data for the benefits and risks of dabigatran versus warfarin in the treatment of nonvalvular atrial fibrillation are lacking. We sought to review real-world observational evidence for the comparative effectiveness and safety of these agents.

Methods and Results—A systematic search of multiple databases was conducted from first available date to March 10, 2015 for longitudinal, observational studies comparing dabigatran with warfarin. Two reviewers evaluated studies for eligibility and extracted hazard ratios for ischemic stroke and gastrointestinal and intracranial bleeding. hazard ratios were pooled using random-effects meta-analysis. Metaregression was performed to assess treatment-effect heterogeneity. We identified 232 unique citations. Seven retrospective cohort studies met study eligibility criteria, with 348 750 patients and a mean follow-up of 2.2 years. In pooled analyses, dabigatran-150 mg was not superior to warfarin in preventing stroke (hazard ratio, 0.92; 95% confidence interval, 0.84–1.01; P=0.066), but had a significantly lower hazard of intracranial bleeding (0.44; 0.34–0.59; P<0.001). Dabigatran-150 mg had a significantly greater hazard of gastrointestinal bleeding than warfarin (1.23; 1.01–1.50; P=0.041), which was potentiated in studies of older (elderly) versus younger populations (median/mean age, ≥75 versus <75 years; β=1.53; 95% confidence interval, 1.10–2.14; P=0.020).

Conclusions—In real-world clinical practice, dabigatran is comparable with warfarin in preventing ischemic stroke among patients with nonvalvular atrial fibrillation. However, dabigatran is associated with a lower risk for intracranial bleeding relative to warfarin, but—particularly among the elderly—a greater risk for gastrointestinal bleeding. Bleeding outcomes from observational studies are consistent with those from the pivotal Randomized Evaluation of Long-Term Anticoagulation Therapy trial. (***Circ Cardiovasc Qual Outcomes*. 2016;9:00-00. DOI: 10.1161/CIRCOUTCOMES.115.002369.**)

Dabigatran in real-world atrial fibrillation

Meta-analysis of observational comparison studies with vitamin K antagonists

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Summary

In the RE-LY clinical trial, dabigatran presented a better effectiveness/safety profile when compared to warfarin. However, clinical trials are not very representative of the real-world setting. We aimed to assess the performance of dabigatran in real-world patients with atrial fibrillation (AF) by means of a systematic review and meta-analysis of observational comparison studies with vitamin K antagonists (VKA). We searched PubMed, Embase and Scopus databases until November 2015 and selected studies according to the following criteria: observational study performed with nonvalvular AF patients; reporting adjusted hazard ratios (HR) of clinical events in a follow-up period; for dabigatran 75 mg, 110 mg or 150 mg versus VKA. Twenty studies were selected which included 711,298 patients, 210,279 of which were treated with dabigatran and the remaining 501,019 with VKA. Ischaemic stroke incidence was of 1.65 /100 patient-years for dabigatran and 2.85/100 patient-years for VKA (HR 0.86, 95 % confidence interval of 0.74–0.99). Major bleeding rate was 3.93/100 patient-years for dabigatran and 5.61/100 patient-years for VKA (0.79, 0.69–0.89). Risk of mortality (0.73, 0.61–0.87) and intracranial bleeding (0.45, 0.38–0.52) were significantly lower in patients treated with dabigatran when compared to patients on VKA. Risk of gastrointestinal (GI) bleeding was significantly higher in patients treated with dabigatran (1.13, 1.00–1.28). No significant difference was observed in risk of myocardial infarction (0.99, 0.89–1.11). In this combined analysis of real-world observational comparison studies with VKA, dabigatran was associated with a lower risk of ischaemic stroke, major bleeding, intracranial bleeding and mortality, higher risk of GI bleeding and a similar risk of myocardial infarction.

Keywords

Atrial fibrillation, dabigatran, vitamin K antagonist, real-world, meta-analysis

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Table 2: Sensitivity analysis for studies performed in the US vs outside the US.

Clinical event	HR and 95 % CI	Interaction p-value
Ischemic stroke		0.790
US	0.89 [0.68, 1.15]	
Outside US	0.83 [0.67, 1.02]	
Myocardial infarction		0.023
US	0.88 [0.79, 0.97]	
Outside US	1.10 [0.96, 1.26]	
Major bleeding		0.049
US	0.99 [0.81, 1.20]	
Outside US	0.75 [0.65, 0.86]	
Intracranial bleeding		0.100
US	0.39 [0.32, 0.48]	
Outside US	0.50 [0.42, 0.61]	
Gastrointestinal bleeding		0.366
US	1.21 [1.02, 1.43]	
Outside US	1.07 [0.88, 1.30]	
Mortality		0.770
US	0.75 [0.60–0.94]	
Outside US	0.71 [0.53–0.94]	

Table 3: Sensitivity analysis for studies with new-user design and studies including experienced VKA patients (Others).

Clinical event	HR and 95 % CI	Interaction p-value
Ischemic stroke		0.150
New-users	0.90 [0.81, 1.01]	
Others	0.67 [0.46, 0.98]	
Myocardial infarction		<0.001
New-users	0.87 [0.79, 0.95]	
Others	1.18 [1.03, 1.34]	
Major bleeding		0.920
New-users	0.78 [0.63, 0.97]	
Others	0.79 [0.70, 0.88]	
Intracranial bleeding		0.002
New-users	0.38 [0.31, 0.45]	
Others	0.57 [0.47, 0.68]	
Gastrointestinal bleeding		0.310
New-users	1.08 [0.91, 1.28]	
Others	1.22 [1.05, 1.42]	
All studies reporting mortality used new-user design.		

“Unreal world” or “real world” data in oral anticoagulant treatment of atrial fibrillation

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The gold standard for studies to change management in clinical practice is the double-blind randomised controlled clinical trial (RCT), or at least an RCT with blinding of the outcome assessment. In 2009, the first large randomised trial of a Non-vitamin K antagonist Oral Anticoagulant (NOAC) in atrial fibrillation (AF), the RELY trial, was published (1). This study compared two doses of dabigatran with warfarin in over 18,000 patients with AF (with blinded endpoint assessment), and although it was a non-inferiority trial, showed a significant reduction in stroke or systemic embolism, but only with the 150 mg BID dose, and less major haemorrhage with the 110 mg BID dose. There was less intracranial haemorrhage with both doses, but more gastro-intestinal bleeding. The warfarin was well controlled, relatively speaking, with a mean time in therapeutic INR range of 64 %. This study led to the licensing of dabigatran for use in AF in many countries from 2010. What this has afforded us now is almost 6 years of experi- or proprietary databases and registries, to provide what has come to be called “real world” data (RWD). Results of these RWD studies have certain advantages over the “unreal world” of RCTs in that they reflect what is actually happening in practice, usually with more liberal inclusion criteria than seen in the pivotal RCTs, and typically providing a broader range of patients with differing stroke risk profiles treated in a broader range of settings. When the results using RWD confirm findings from the RCTs, it provides the clinician with some confidence about the generalisability of RCT findings that are used to formulate recommendations in treatment guidelines.

There are a number of important limitations to analyses of RWD of NOACs, in that patients given the newer drug may differ in important ways from those given warfarin or other vitamin K antagonists (VKA) when the choice is up to the clinician. Some of these differences may be subtle and very difficult to discern using demographics and clinical characteristics only in the USA). In most other parts of the world, the 110 mg BID dose is available and widely used. In Europe the 150 mg BID dose is recommended for most patients according to the European label, while the 110 mg BID dose is recommended for older individuals ≥80 years or with higher bleeding risk (HASBLED score ≥3) or with concomitant verapamil. Simulations of use of the European label using the RELY RCT data yielded interesting extrapolations (6), showing superiority in both efficacy (stroke/systemic embolism and mortality) and safety (major bleeding) and a net clinical benefit compared to warfarin. RWD with much larger numbers would be useful to determine whether this advantage might be seen in everyday practice.

It is therefore of interest to have a large systematic review and meta-analysis of dabigatran RWD in AF performed, and published in this issue of the journal (7). There have been previous meta-analyses by the same authors (published in abstract form only) and this year by Romanelli et al.

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

METHODS

In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

From the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (S.J.C., S.Y., J.E., J.P., E.T.); Lankenau Institute for Medical Research and the Heart Center, Wynnewood, PA (M.D.E., A.P.); Uppsala Clinical Research Center, Uppsala, Sweden (J.O., L.W.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (P.A.R., J.V., S.W.); Working Group on Cardiovascular Research the Netherlands, Utrecht, the Netherlands (M.A.); St. John's National Academy of Health Sciences,

RESULTS

Rates of the primary outcome were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% confidence interval [CI], 0.74 to 1.11; P<0.001 for noninferiority) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.66; 95% CI, 0.53 to 0.82; P<0.001 for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran (P=0.003) and 3.11% per year in the group receiving 150 mg of dabigatran (P=0.31). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran (P<0.001) and 0.10% per year with 150 mg of dabigatran (P<0.001). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran (P=0.13) and 3.64% per year with 150 mg of dabigatran (P=0.051).

CONCLUSIONS

In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)

Beijing (J.Z.); Estudios Clínicos Latinoamérica, Rosario, Argentina (R.D.); Lady Davis Carmel Medical Center, Haifa, Israel (B.S.L.); Vivantes Klinikum Neukölln, Berlin (H.D.); University Duisburg-Essen, Essen, Germany (H.-C.D.); and Sunnybrook Health Sciences Centre, Toronto (C.D.J.). Address reprint requests to Dr. Connolly at the Population Health Research Institute, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at connostu@phri.ca.

*Members of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Study Group are listed in the Appendix and the Supplementary Appendix, available with the full text of this article at NEJM.org.

Drs. Connolly, Ezekowitz, Yusuf, and Wallentin contributed equally to this article.

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Table 2. Efficacy Outcomes, According to Treatment Group.

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	%/yr	*no. of patients*	%/yr	*no. of patients*	%/yr						
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58–0.91)	0.005
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001	0.70 (0.56–0.89)	0.003
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001	0.85 (0.39–1.83)	0.67
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03	0.69 (0.54–0.88)	0.002
Nondisabling stroke	60	0.50	44	0.37	69	0.58	0.86 (0.61–1.22)	0.40	0.62 (0.43–0.91)	0.01	0.72 (0.49–1.07)	0.10
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005	0.70 (0.53–0.94)	0.02
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048	1.02 (0.76–1.38)	0.88
Pulmonary embolism	14	0.12	18	0.15	11	0.09	1.26 (0.57–2.78)	0.56	1.61 (0.76–3.42)	0.21	1.27 (0.63–2.56)	0.50
Hospitalization	2311	19.4	2430	20.2	2458	20.8	0.92 (0.87–0.97)	0.003	0.97 (0.92–1.03)	0.34	1.06 (1.00–1.12)	0.04
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04	0.94 (0.79–1.11)	0.44
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66

Non-inferiority trials are unethical because they disregard patients' interests

Silvio Garattini, Vittorio Bertele'

Equivalence trials[1] have been widely used to assess new drugs, but have recently lost ground to a non-inferiority design. This type of trial is usually accepted by regulatory authorities for approval of new drugs or new indications, although the US Food and Drugs Administration has raised some concerns.[2] In this paper, we argue that the scientific community should ban non-inferiority and equivalence trials because they are unethical, whatever measures are taken to prevent their methodological pitfalls and inappropriate interpretation of results.[3–8] Exceptions might exist, but we could not identify a situation in which patients can justifiably be entered into a trial that will not provide them with any advantage.

Pretext for looking for non-inferiority

Use of equivalence or non-inferiority rather than superiority designs implies the intention of not trying to prove any additional value of new drugs. However, the declared aim is to expand treatment options for patients with poor tolerance of, or no response to, available products. Drug producers argue that there is no reason to define the benefit-risk profile of new agents as better but not to the extent that it is recognised as such. For example, if the non-inferiority limit is set at 7·5%, an increase in the incidence of serious events or deaths—say 7% instead of the 5% currently established for the comparator—is not seen as large enough to mark a difference between the new and the control drug. The new drug will therefore be considered non-inferior to the old drug, even if in 1000 patients treated with the former, there could be 20 more deaths than with the latter.

These arguments also apply to equivalence trials, which aim to prove similarity of a new drug to the comparator, since true equivalence is theoretical and is difficult to demonstrate. Equivalence means that a new drug is not much worse than the comparator (as in non-inferiority trials), but also is not much better. Similarity is defined by limits that include a superiority margin as well as a non-inferiority margin. Since equivalence trials explore the differences between control and study treatments in both directions, they provide a more reliable estimate of the relative efficacy of two treatments than do non-inferiority trials. However, use of a non-inferiority

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Commercial aims, not patients' interests

Are there specific reasons for allowing a non-inferiority approach? One reason cited is that for patients who do not respond to existing treatments, products with similar activity could offer a useful alternative. The aim is reasonable, but the approach is not. If the target is non-responders to current treatments, why not test the new agents' superiority in this subset, rather than its non-inferiority in the overall population? This approach would meet patients' needs best, but restricts the market that can be targeted by the drug companies.

Another suggested reason is that non-inferior drugs might be better tolerated or easier to use than existing treatments. However, these features are unlikely to be confirmed in non-inferiority trials, since any advantage should translate into better compliance and result in a superior rather than a non-inferior outcome.

Superiority trials are also said to generally take much longer and require many more patients than do non-inferiority trials, delaying the availability of potentially useful drugs. However, non-inferiority trials do not necessarily need a smaller sample size, which can be the result of selecting a large inferiority margin or of other questionable methodological choices.[1] Moreover, it is our view that a delay in the availability of proven effective drugs is preferable to early availability of potentially advantageous drugs whose real efficacy has not been formally established. Actual efficacy testing might never be done, particularly if patients no longer agree to be randomly assigned to older drugs.

Enrolling patients in non-inferiority trials betrays their trust

We believe that non-inferiority studies have no ethical justification, since they do not offer any possible advantage to present and future patients, and they disregard patients' interests in favour of commercial ones. This situation betrays the agreement between patients and researchers set out in any fair informed consent form that presents randomised trials as the only ethical way to address clinical uncertainty. Non-inferiority trials claim minor advantages for the test drugs, but do not prove their efficacy compared with older products. Few patients would agree to participate if this message were clear in the informed consent form: as we said before, why should patients accept a treatment that, at best, is not worse, but could actually be less effective or less safe than available treatments?[15]

In conclusion, we believe that non-inferiority trials fail to meet the commitments of good clinical research: "Ask an important question, and answer it reliably".[16] Although a non-inferiority study reduces research and development costs and commercial risks thereafter, it asks no relevant clinical questions. Randomisation should not even be allowed in such trials, since it is unethical to leave to chance whether patients receive a treatment that is anticipated to provide no extra benefit, but could be less safe and less effective than existing treatment options.

With regard to the reliability of the methods and consequently of the results, the uncertainty surrounding

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Studi di non inferiorità e di equivalenza: limiti e ambiguità

L'incertezza del trattamento come fondamento del trial

La sperimentazione clinica randomizzata e controllata (Randomized Controlled Trial, RCT), universalmente accettata come gold standard della ricerca medica, prevede il confronto di due trattamenti per verificare se essi si equivalgano oppure se uno dei due risulti migliore.

Nel progettare qualsiasi trial clinico non si può prescindere da un principio etico e scientifico fondamentale: il "principio di incertezza". Infatti uno studio clinico è giustificato unicamente se il paziente e il medico sono incerti circa il trattamento da adottare tra quelli dimostrata, implica la superiorità del nuovo trattamento.

Obiettivo degli studi di non inferiorità è quello di dimostrare che un nuovo trattamento non sia peggiore rispetto a quello di confronto, stabilendo a priori una differenza limite ($-\Delta - 0$), che si possa considerare irrilevante dal punto di vista clinico, che permetta di considerare il nuovo intervento non inferiore rispetto a quello di confronto.

Analogamente, attraverso uno studio di equivalenza si vuole verificare se i due interventi indagati presentino lo stesso profilo di efficacia e/o di sicurezza, predefinendo la massima differenza ($-\Delta$ a $+\Delta$), clinicamente non rilevante, che consenta di ritenere i due trattamenti sovrapponibili[2].

un elevato numero di drop-out (pazienti che si sono ritirati dallo studio) e di missing data, l'ITT tenderebbe ad escludere la presenza di una differenza tra i trattamenti indagati (effetto sfortunatamente spesso frequente in questi studi). Più imprevedibile risulta essere la direzione (pro o contro la non differenza/equivalenza dei trattamenti) dell'analisi PP, influenzata soprattutto dallo sbilanciamento dei due bracci dovuto ad eventuali differenti percentuali e cause del drop-out[2].

A causa della flessibilità del disegno i trial di non inferiorità/equivalenza presentano un elevato rischio di manipolazione dei risultati. Ad esempio, è stato dimostrato che nel 62% dei report relativi a questi studi l'outcome primario era stato cambiato, introdotto ex novo oppure omesso. Analogamente l'entità del Δ, che deve essere fissata a priori, viene spesso aumentata per nascondere il fatto che il nuovo trattamento si è dimostrato inferiore a quello di confronto[3].

Infine, non di rado, studi inizialmente progettati per essere studi di superiorità vengono successivamente presentati come trial di equivalenza/non inferiorità qualora non sia stato possibile dimostrare la superiorità del nuovo intervento. A tale proposito potrebbe risultare con il tempo rischiosa la posizione assunta dall'autorità regolatoria europea (EMEA) che dichiara accettabile, sebbene in situazioni "estreme", l'adozione di un disegno di superiorità con un livello di significatività superiore allo 0,05 quale alternativa alla definizione di un Δ di non inferiorità[4].

Gli studi di non inferiorità/equivalenza presentano forti elementi di ambiguità che vanno tenuti presenti da tutti gli attori (comitati etici, sperimentatori clinici, editori) coinvolti a vario titolo nella loro progettazione, valutazione, reclutamento dei pazienti, conduzione, presentazione dei dati, trasferimento dei risultati alla pratica clinica. Un aspetto particolarmente delicato e ambiguo di questo tipo di studi è rappresentato dall'informazione destinata ai pazienti cui viene proposta la partecipazione a questi studi. Attualmente il testo del "consenso informato" viene formulato allo stesso modo per gli studi di superiorità e per quelli di non inferiorità/equivalenza. Tuttavia i due tipi di studi hanno obiettivi decisamente diversi, pertanto servirsi della stessa "formula" di consenso informato potrebbe non essere ritenuto etico da tutti. Nel caso dei trial di superiorità bisognerebbe prevedere l'affermazione che "il nuovo trattamento potrà dimostrarsi migliore, uguale o peggiore rispetto a quello di confronto", mentre chi partecipa ad uno studio di non inferiorità/equivalenza deve essere messo al corrente che potrebbe andare incontro a rischi, senza che la ricerca si proponga alcun vantaggio clinico o, qualora vi fosse, il disegno sperimentale potrebbe non essere in grado di rivelarlo. I pazienti dovrebbero sapere se lo studio a cui partecipano non è in grado di fornire alcun vantaggio clinico, ma è condotto con scopi puramente commerciali[7].

EDITORIALS

Can We Rely on RE-LY?

Brian F. Gage, M.D.

In patients with atrial fibrillation, warfarin prevents 64% of strokes.[1] Thus, warfarin has become the recommended treatment for candidates for anticoagulation therapy who have atrial fibrillation and at least one additional risk factor for stroke.[2]

Despite clear and consistent recommendations,[3] warfarin is prescribed to only two thirds of appropriate candidates.[4] Several factors contribute to suboptimal use of warfarin therapy:

cause warfarin use was not blinded and patients taking warfarin had regular follow-up evaluations for purposes of INR monitoring, reporting bias could have affected the detection of outcome events. To minimize this risk, each event was adjudicated by two independent investigators who were unaware of the treatment assignments, and all hospital records were reviewed to ensure complete detection of events.

The primary outcome of RE-LY was systemic

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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

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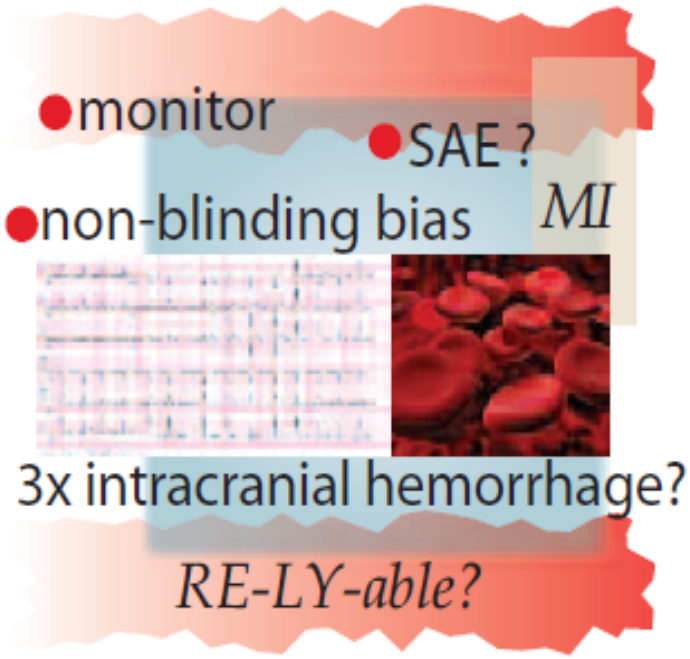
Dabigatran for atrial fibrillation
Why we can not rely on RE-LY



Dabigatran (Pradax®), a direct thrombin inhibitor oral anticoagulant, was licensed in Canada in November 2010 for stroke prevention in patients with non-valvular atrial fibrillation. It is being promoted as an alternative to warfarin with the purported advantage that coagulation monitoring is not required. Do we know enough about dabigatran? It took over 50 years to learn how to use warfarin with reasonable effectiveness and safety for this use.

Health Canada approved dabigatran for this indication largely based on data from the RE-LY trial.[1]

The objective of this Letter is to provide a detailed analysis of the RE-LY trial data from the NEJM paper[1] as well as the more complete data from the US FDA website[2]. Our analysis applies the same hierarchy of health outcomes presented in previous Therapeutics Letters.

The RE-LY trial performed a double-blind comparison between two doses of dabigatran and a non-blinded comparison between dabigatran and warfarin. For the

an estimate of net health benefit; the numerical difference (1.6%) favouring the lower dose barely misses statistical significance. Based on its benefit for stroke, both the FDA and Health Canada approved only the 150 mg BID dose of dabigatran for patients with non-valvular atrial fibrillation[3]; the European Medicines Agency approved both 150 and 110 mg BID[4]. Alternative interpretations of the data shown in Table 1 are that 110 mg BID provides a net health benefit over 150 mg BID, or that this single trial has not established the optimal dose of dabigatran.

Table 2 shows key outcomes by hierarchy for the

The RE-LY trial performed a double-blind comparison between two doses of dabigatran and a non-blinded comparison between dabigatran and warfarin. For the blinded dose comparison, Table 1 shows key health outcomes ranked from most to least severe, using data from both sources.

Table 1: Key outcomes for dabigatran 110 vs 150 mg BID

Outcome	Dabigatran 110mg BID	Dabigatran 150mg BID	RR [95% CI]	ARR ARI
Patients randomized	6015	6076		
Deaths	446	444	1.01	
(FDA)	7.4%	7.3%	[0.89, 1.15]	
Serious adverse events	Not reported	Not reported	?	?
Hospitalizations	2311	2430	0.96	
(NEJM)	38.4%	40%	[0.92, 1.00]	
Disabling and fatal stroke	89	61	1.47	0.5%
(FDA)	1.5%	1%	[1.07, 2.04]	
Intracranial hemorrhage	27	38	0.72	
(FDA)	0.4%	0.6%	[0.44, 1.17]	
MI	86	89	0.98	
(NEJM)	1.4%	1.5%	[0.73, 1.31]	
Bleeds leading to hospitalization minus intracranial hemorrhage (FDA)	259	330	0.79	1.1%
	4.3%	5.4%	[0.68, 0.93]	

Dabigatran 150 mg BID reduced fatal and disabling strokes by 0.5% compared with 110 mg BID and reduced all ischemic strokes by 0.8% (not shown). However, dabigatran 150 mg BID was also more harmful, causing a 1.1% absolute increase in bleeding leading to hospitalization. Total hospitalizations provides

150 mg BID, or that this single trial has not established the optimal dose of dabigatran.

Table 2 shows key outcomes by hierarchy for the unblinded comparison between warfarin and the combined doses of dabigatran, as it is not clear which of the two doses is the best.

This analysis suggests a possible benefit of dabigatran over warfarin. Warfarin is associated with a trend toward increased mortality and increases the risk of any hospitalization by 1.6%.

However, the comparison between warfarin and dabigatran was **not blinded** and thus all outcomes are subject to performance and ascertainment bias favouring dabigatran. This interpretation is reinforced by the FDA review, which found that lack of blinding of patients and clinicians led to 'differential treatment of patients during the study period' (performance bias) and that the presence of ascertainment and adjudication bias was sufficient to overturn the claim of a stroke benefit for dabigatran 150 mg BID as compared with warfarin[2]. Furthermore the FDA clinical reviewer found that the trend toward increased mortality with warfarin was entirely due to investigator sites where INR monitoring was inferior. At sites where INR was within therapeutic range ≥ 67% of the time, relative risk for mortality (RR 1.05) favoured warfarin over dabigatran.[2]

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Why did warfarin increase intracranial hemorrhage 3-fold compared with the annualized rate for dabigatran of 0.27% per year? The annualized incidence of intracranial hemorrhage was lower in atrial fibrillation patients taking warfarin during comparable recent trials: 0.53% in SPORTIF III[5], 0.28% in SPORTIF V[6] and 0.3% or 0.45% in two Cochrane reviews[7,8]. These comparisons suggest something unusual about the warfarin arm in the RE-LY trial.

Additional observations

Absence of blinding in experiments creates a high risk of bias. This was amply demonstrated with ximelagatran, an earlier direct thrombin inhibitor that did not receive regulatory approval. In SPORTIF III, an unblinded clinical trial similar to RE-LY, ximelagatran was associated with numerically fewer strokes/systemic emboli versus warfarin, RR 0.71 [0.48, 1.07].[5] However, SPORTIF V, a follow-up double blinded trial, showed numerically greater strokes/systemic embolic for ximelagatran, RR 1.38 [0.91, 2.10].[6]

The use of antiplatelet agents in addition to anticoagulants was surprisingly prevalent in all 3 arms of the RE-LY trial. During the trial approximately 40% of patients took aspirin and 7% took clopidogrel at some time. Taking either antiplatelet drug doubled the incidence of major bleeding events, an absolute increase of > 2% per year. This effect was similar for both doses of dabigatran and for warfarin.

Any adverse effect (FDA)	5445 78.1%	4531 75.6%	1.03 [1.02, 1.05]	2.5%
Dyspepsia (NEJM)	1395 11.5%	348 5.8%	2.00 [1.78, 2.24]	5.7%

Conclusions

- **Licensing of dabigatran 150 mg BID for atrial fibrillation is premature, pharmacologically irrational and unsafe for many patients.**
- The optimal dose of dabigatran for non-valvular atrial fibrillation is not yet clear.
- An independent audit of RE-LY is needed to check for irregularities in conduct, sources of bias and the cause of the unusually high incidence of intracranial hemorrhage in the warfarin arm.
- An independently conducted double-blind RCT comparing dabigatran with warfarin in patients with non-valvular atrial fibrillation is required.
- **Taking antiplatelet drugs in combination with oral anticoagulants doubles the incidence of major bleeding events.**

The draft of this Therapeutics Letter was submitted for review to 60 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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Warfarin or dabigatran for treatment of atrial fibrillation

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Summary. *Background:* New antithrombotic drugs for prevention and treatment of thromboembolic disorders in AF that are less demanding on local staff and facilities than warfarin should be welcomed if proved successful. *Objectives:* The comparative value and possible dangers of substituting the new drug dabigatran as a replacement remain to be established. Its safety and effectiveness must be reviewed and assessed by further study. *Methods:* Clinical results of the European Action on Anticoagulation (EAA) computer-assisted dosage study and the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial have been compared. *Results:* Clinical events were lower in patients on warfarin in the EAA study compared to patients on both warfarin and dabigatran in the RE-LY study. *Conclusion:* Evaluations should recognize optimum requirements for safe and effective administration of both types of drug. In the warfarin arm improvements in effectiveness and safety recently introduced (i.e. the PT/INR line and variance growth analysis) should be included as they have been shown to be successful in improved prediction of bleeding and further thromboembolism. The incidence of bleeding with dabiga-

Introduction

Atrial fibrillation (AF) is the commonest indication for oral anticoagulation. On a world scale the most widely-used treatment, warfarin, presents problems because of its demands. A great disadvantage is the need for dependable laboratory monitoring.

International normalized ratio (INR) testing is required to ensure patients are within the target therapeutic range, usually 2.0–3.0 INR. This is usually achieved for only about half to two-thirds of the time, limiting benefits and safety [1]. A further constraint is the need for the INR to be in accord with the WHO scheme for oral anticoagulant control [2]. This requires a WHO or equivalent international reference preparation (IRP), thromboplastin, to standardize INR testing, now universally automated but formerly based on the manual prothrombin time (PT).

Because of attendant difficulties (e.g. the need for large numbers of normal and patients' blood samples and the availability of reference thromboplastins) and because of variations caused by locally used coagulometers, International Sensitivity Index (ISI) calibration is now rarely per-

Table 1 Comparative results with warfarin and dabigatran in the RE-LY and EAA studies

	RE-LY study warfarin	Dabigatran		EAA study warfarin
		110 mg	150 mg	
Patients, total	6022	6015	6076	5939
Patients per centre	6.3			182.5
Average age	72			72
Starting anticoagulants, %	50			79
Overall events (% per year)				
Stroke	1.57	1.44	1.01	0.30
Major bleeding	3.36	2.71	3.11	0.86
Minor bleeding	16.37	13.16	14.84	2.70
Deaths per year	4.13	3.75	3.64	0.75

RE-LY and EAA studies

	RE-LY study warfarin	Dabigatran		EAA study warfarin
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Minor bleeding	16.37	13.16	14.84	2.70
Deaths per year	4.13	3.75	3.64	0.75

spread over 951 centres. Only in the EAA study was the reliability of reported INR at participant centres checked by centrally organized local ISI calibrations and by external quality control of reported INR.

The RE-LY patients were randomized to three groups (i.e. warfarin compared with two different dosage regimes of dabigatran (110 and 150 mg)) [3]. Unlike the EAA investigation there were no reported listed local procedures to check the reliability of the resultant INR.

Clinical events in the EAA patients on warfarin were lower than for warfarin patients with both dose regimens of dabigatran in the RE-LY study (see Table 1), although the reported 'time in target INR range' was only marginally higher. Morbidity and mortality were much higher in RE-LY in all three groups than with warfarin in the EAA study and better results were obtained with both dabigatran regimes than with warfarin.

Comparative results of RE-LY and EAA studies

Table 1 shows the RE-LY outcomes with warfarin and

substantially greater success. In RE-LY two important assessments of INR control (i.e. local ISI calibration and external quality control of INR) were not reported. We propose that this may be one of the reasons explaining why the EAA warfarinised patients suffered considerably less thrombotic and bleeding episodes.

The INR system has proved difficult to implement reliably worldwide for many reasons; for example, its complex demands, particularly the WHO protocol requirements, the need for the availability of reference reagents of human, rabbit or bovine origin for ISI calibration, considerable local blood donations (plasma samples from 60 warfarin-treated patients and 20 normal subjects tested at several centres), and the need for relevant species reference thromboplastins and for ISI calibration manual prothrombin time testing, now almost universally discarded, which is an essential part of the EAA study and now mainly devolved to reagent manufacturers [10,11].

Manufacturers' ISIs and INRs, however, cannot be guaranteed to reflect local values as, for example, coagulometer calibration ISIs are required and INRs often vary with coagulometers even of the same model and manufacturer used in the same laboratory [12,13]. In RE-LY there was no method reported of checking the reliability of local ISIs and INRs and there was only a recruitment of 6.3 patients per centre against the EAA's 182. The larger number of centres participating in the RE-LY study compared with the EAA study would result in greater between-centre variation in the quality of oral anticoagulant treatment (OAT) and this could also be another reason for the lower number of thrombotic and bleeding episodes. The higher incidence of events in the RE-LY study may have been at less experienced clinical centres and a subgroup analysis stratifying centres by size or proficiency may prove this. Though the aims of the two stud-

cated by the ESC Task Force on Anticoagulants' [15], which stated that it achieves reliable INR without the need for local ISI calibrations. Hopefully any further comparison of dabigatran or other new anticoagulants with warfarin will incorporate this method. The EAA PT/INR line test plasmas are now available internationally in a five-plasma kit.

2 A variable growth rate (VGR) analysis was shown in a 2013 EAA report to be of greater value than the previously accepted 'time in INR range', in predicting 'clinical events' during warfarin treatment [16,17]. Different types of VGR were used to analyse results in the EAA multicentre study and one proved more dependable than simple INR or 'time in INR range' in predicting clinical events, the latter being previously considered the best guide to the risk of clinical events.

INR results from 32 EAA centres mainly in Europe were checked by independent ISI calibration and external quality assessment but in the RE-LY study these checks were not reported. Although there was an insignificant difference in mean time in INR range in the two studies, INR was shown to be a weaker predictor of clinical events than VGR in the EAA study, particularly in short-term OAT (9).

Future investigations should include measures to ensure the safest and most effective administration of both study drugs, and for warfarin, the above two relatively simple control procedures introduced recently by the EAA. These should be an essential part of future studies of the control of warfarin dosage in AF. The precise incidence of bleeding complications with dabigatran for which there is no established antidote will require careful evaluation.

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INR derivation with the PT/INR Line simplified using a spreadsheet from the world wide web

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ABSTRACT

Background The prothrombin time/international normalised ratio (PT/INR) Line method to derive INR, based on only five European Concerted Action on Anticoagulation (ECAA) certified plasmas, is shown to be reliable in previous ECAA studies. A simpler method not requiring linear regression calculation would be an advantage.

Method After determining the local PT/INR Line, local INRs have been obtained using a readily available spreadsheet on the internet which laboratories can use without performing any additional calculations.

Results Examples of INR derivation have been obtained from results at 16 centres using a range of local coagulometers with human thromboplastin international reference preparations (IRPs). The procedure does not require manual PT testing, local international sensitivity index calibration, availability of thromboplastin IRPs or local mean normal prothrombin time.

Conclusions From the PT/INR Line, INR values for local PT results are easily obtained using an Excel spreadsheet from our website (http://www.anticoagulants.co.uk/).

The PT/INR Line based on only five certified European Concerted Action on Anticoagulation (ECAA) plasmas does not involve manual PT testing, multicentre ISI calibration or determination of local mean normal prothrombin time (MNPT). In the present report, a further simplification of INR derivation is described based on an Excel spreadsheet available from the first author's website at http://www.anticoagulants.co.uk/. The spreadsheet enables a user to directly perform the PT/INR Line with ease and can be used freely as a guide to the procedure.

MATERIALS AND METHODS

This procedure for INR derivation using the PT/INR Line[2–4] does not require the following:

1. outdated manual PT testing;
2. multicentre local ISI determination using the relevant thromboplastin IRP;
3. local MNPT;
4. relatively complex orthogonal/linear regression

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To obtain local INR with the PT/INR Line simply enter local PT values with the 5 calibrant plasmas into box corresponding with certified INR and the program will calculate local INR for patient plasmas

1ST STEP

Insert manually certified INR values (Human, Rabbit or Bovine thromboplastin IRP from Table) and enter local PT of the 5 calibrant plasmas in the green box (example of INR derivation shown below [Poller et al. 2010#]).

Plasmas	Certifed INR	Local PT (secs)
1	2,36	26
2	2,99	35,9
3	2,03	20
4	3,73	38,6
5	2,64	31

Poller L, Ibrahim S, Keown M, Pattison A, Jespersen J. A simplified method for International Normalised Ratio (INR) derivation based on the prothrombin time / INR Line – An International study. Clin Chem 2010; 56:10:1608-17.

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	A	B	C	D	E	F
22						
23						
24	2ND STEP					
25		To obtain INR on a test (patient) plasma insert PT (e.g 25 seconds) into the box				
26						
27		PT (secs):	25			
28						
29		INR =	2,31		INR from ISI and MNPT	2,31
30						
31	**Table of INR values**					
32	**Users can devise a table with a range of observed PT results and corresponding INR values or you can use the PT/INR ISI and MNPT to derive INR with coagulometers**					
33	Example	Observed PT	INR			
34		15	1,45			
35		20	1,88			
36		25	2,31			
37		30	2,73			
38		35	3,15			
39		40	3,56			

The clinical evaluation of International Normalized Ratio variability and control in conventional oral anticoagulant administration by use of the variance growth rate

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Summary. *Introduction:* The time in target International Normalized Ratio (INR) range (TIR) is used to assess the control and intensity of oral anticoagulation, but it does not measure variation in the INR. *Objectives:* The value of assessing INR variability by use of the variance growth rate (VGR) as a predictor of events was investigated in patients treated with warfarin. *Methods:* Three different methods of VGR determination (A, B1, and B2) together with the TIR were studied. Method A measures both INR variability and control, but methods B1 and B2 measure variability only. The VGR and TIR were determined over three time periods: overall follow-up to an event, and 6 months and 3 months before an event. *Results:* Six hundred and sixty-one control patients were matched to 158 cases (bleeding, thromboembolism, or death). With all VGR methods, the risk of an event was greater in unstable patients at 6 months before an event than in stable patients. Method A demonstrated the greatest risk 3 months before an event in the unstable VGR group as compared with the stable group (odds ratio 3.3, 95% confidence interval 1.9–5.7, $P < 0.005$). The risk of an event was 1.9 times greater in patients with a low TIR (< 39%) than in those with a high TIR (> 80%) in the 3-month period ($P = 0.02$). Risk of bleeding was significantly greater in the 3-month period in patients with unstable VGR, with the greatest risk found with method B2 ($P < 0.01$). *Conclusions:* Patients with unstable anticoagulation have a significantly increased risk of 'clinical events' at 3 and 6 months before an event. The VGR can be incorporated into computer-dosage programs, and may offer additional safety when oral anticoagulation is monitored.

Keywords: analysis of variance, antithrombotic agents, International Normalized Ratio, Marevan, warfarin.

Introduction

Despite the recent development of new anticoagulant drugs that are not vitamin K antagonists, e.g. dabigatran and rivaroxaban, warfarin remains by far the most widely used, and is likely to remain so for a considerable time. In all reports so far published, however, despite the reported benefit of oral anticoagulation, with considerable clinical gain, there have always been an important number of 'clinical events' of bleeding and further thromboembolism during treatment with warfarin and allied vitamin K antagonists.

In most studies of oral anticoagulant administration, clinical event data are most commonly reported as the primary endpoint alongside the percentage time in the target International Normalized Ratio (INR) range (TIR [or TTR in some studies]) to assess the effectiveness of oral anticoagulation. However, the TIR describes only the control and intensity of anticoagulation, and the

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Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

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ABSTRACT

BACKGROUND

The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment. Rivaroxaban, an oral factor Xa inhibitor, may provide more consistent and predictable anticoagulation than warfarin.

From the Duke Clinical Research Institute (M.R.P., K.W.M., J.G., J.P.P., R.C.B.) and Duke Translational Medicine Institute (R.M.C.), Duke University Medical Center, Durham, NC; Johnson & Johnson Pharmaceutical Research and Development

METHODS

In a double-blind trial, we randomly assigned 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism.

RESULTS

In the primary analysis, the primary end point occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority). In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P<0.001 for noninferiority; P=0.12 for superiority). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (hazard ratio, 1.03; 95% CI, 0.96 to 1.11; P=0.44), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, P=0.02) and fatal bleeding (0.2% vs. 0.5%, P=0.003) in the rivaroxaban group.

CONCLUSIONS

In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. (Funded by Johnson & Johnson and Bayer; ROCKET AF ClinicalTrials.gov number, NCT00403767.)

Raritan (G.P., C.C.N.), and Bayer HealthCare Pharmaceuticals, Montville (J.F.P., S.D.B.) — both in New Jersey; Massachusetts General Hospital and Harvard Medical School — both in Boston (D.E.S.); Ruprecht-Karls-University, Heidelberg (W.H.), and Hospital of the University of Münster, Münster (G.B.) — both in Germany; the Cardiovascular Institute, Mount Sinai Medical Center, New York (J.L.H.); Royal Perth Hospital, Perth, WA, Australia (G.J.H.); and the University of Edinburgh and Royal Infirmary of Edinburgh — both in Edinburgh (K.A.A.F.). Address reprint requests to Dr. Patel at Duke Clinical Research Institute, Duke University Medical Center, Rm. 0311 Terrace Level, 2400 Pratt St., Durham, NC 27705, or at manesh.patel@duke.edu.

*A complete listing of the steering committee members and trial investigators in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) is provided in the Supplementary Appendix, available at NEJM.org.

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N Engl J Med 2011;365:883-91.

Table 2. Primary End Point of Stroke or Systemic Embolism.*

Study Population	Rivaroxaban			Warfarin			Hazard Ratio (95% CI)†	P Value	
	No. of Patients	No. of Events	Event Rate *no./100 patient-yr*	No. of Patients	No. of Events	Event Rate *no./100 patient-yr*		Noninferiority	Superiority
Per-protocol, as-treated population‡	6958	188	1.7	7004	241	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	7061	189	1.7	7082	243	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	7081	269	2.1	7090	306	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment		188	1.7		240	2.2	0.79 (0.66–0.96)		0.02
After discontinuation		81	4.7		66	4.3	1.10 (0.79–1.52)		0.58

* The median follow-up period was 590 days for the per-protocol, as-treated population during treatment; 590 days for the safety, as-treated population during treatment; and 707 days for the intention-to-treat population.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group.
‡ The primary analysis was performed in the as-treated, per-protocol population during treatment.
§ Follow-up in the intention-to-treat population continued until notification of study termination.

Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events	Event Rate	Events	Event Rate		
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

* All analyses of rates of bleeding are based on the first event in the safety population during treatment.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group and were calculated with the use of Cox proportional-hazards models with the study group as a covariate.
‡ Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.
§ Minimal bleeding events were not included in the principal safety end point.
¶ Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

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Factors Associated With Major Bleeding Events

Insights From the ROCKET AF Trial (Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)

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Objectives This study sought to report additional safety results from the ROCKET AF (Rivaroxaban Once-daily oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation).

Background The ROCKET AF trial demonstrated similar risks of stroke/systemic embolism and major/nonmajor clinically relevant bleeding (principal safety endpoint) with rivaroxaban and warfarin.

Methods The risk of the principal safety and component bleeding endpoints with rivaroxaban versus warfarin were compared, and factors associated with major bleeding were examined in a multivariable model.

Results The principal safety endpoint was similar in the rivaroxaban and warfarin groups (14.9 vs. 14.5 events/100 patient-years; hazard ratio: 1.03; 95% confidence interval: 0.96 to 1.11). Major bleeding risk increased with age, but there were no differences between treatments in each age category (<65, 65 to 74, ≥75 years; $p_{interaction} = 0.59$). Compared with those without (n = 13,455), patients with a major bleed (n = 781) were more likely to be older, current/prior smokers, have prior gastrointestinal (GI) bleeding, mild anemia, and a lower calculated creatinine clearance and less likely to be female or have a prior stroke/transient ischemic attack. Increasing age, baseline diastolic blood pressure (DBP) ≥90 mm Hg, history of chronic obstructive pulmonary disease or GI bleeding, prior acetylsalicylic acid use, and anemia were independently associated with major bleeding risk; female sex and DBP <90 mm Hg were associated with a decreased risk.

Conclusions Rivaroxaban and warfarin had similar risk for major/nonmajor clinically relevant bleeding. Age, sex, DBP, prior GI bleeding, prior acetylsalicylic acid use, and anemia were associated with the risk of major bleeding. (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation: NCT00403767) (J Am Coll Cardiol 2014;63:891–900)

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warfarin (active or placebo) dose was reduced in 116 (4%) patients. The study drug was temporarily discontinued but then restarted in 1,337 (46.2%) and permanently discontinued in 381 (13.1%). Bleeding led to permanent study drug discontinuation in 322 (4.5%) rivaroxaban and 286 (4%) warfarin patients (absolute difference 0.5; 95% CI: −0.2 to 1.2).

Major bleeding. Figure 2 presents the HRs for major bleeding in patients randomized to receive rivaroxaban compared with warfarin in key subgroups according to patient baseline characteristics. The risk of major bleeding increased with increasing age, although there were no interaction = 0.34). The relative risk of intracranial hemorrhage for rivaroxaban versus warfarin was statistically significantly lower in those under 75 years (0.37% vs. 0.68%; HR: 0.54; 95% CI: 0.33 to 0.89) and numerically lower in those 75 years or older (0.66% vs. 0.83%; HR: 0.80; 95% CI: 0.50 to 1.28) (p value for interaction = 0.27). There was a statistically significant p value for interaction when comparing the HRs for major bleeding across regions, with the North American cohort having the highest overall rates, including a significantly higher frequency in the rivaroxaban-treated patients (7.1% vs. 5.0%; HR: 1.43; 95% CI: 1.12 to 1.82).

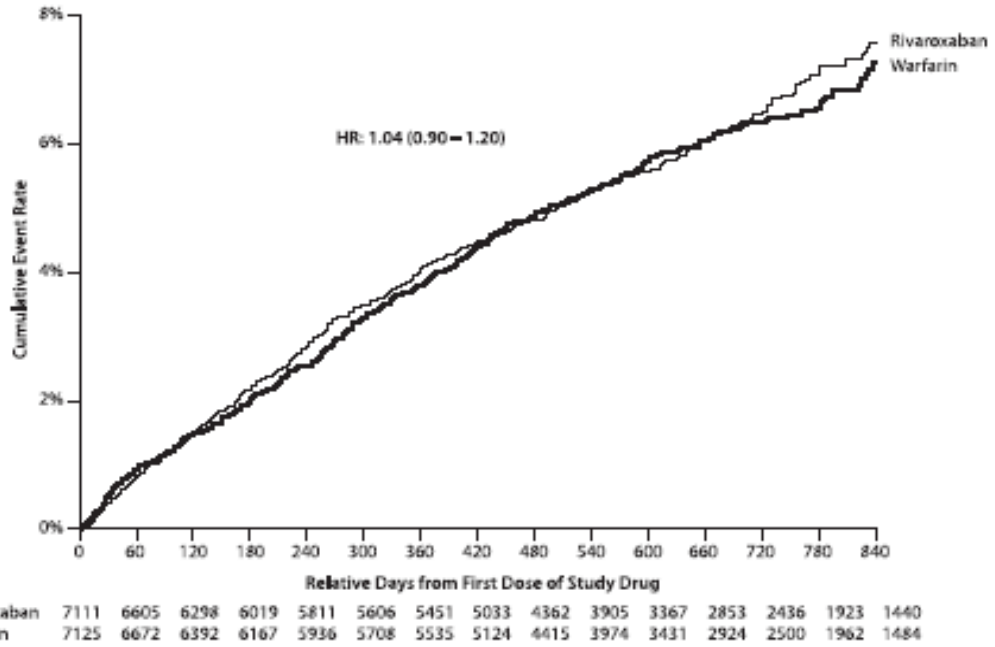

Figure 1 Major Bleeding by Treatment

Kaplan-Meier curves for major bleeding for the treatment groups. HR = hazard ratio.

Impact of Global Geographic Region on Time in Therapeutic Range on Warfarin Anticoagulant Therapy: Data From the ROCKET AF Clinical Trial

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Background—Vitamin K antagonist (VKA) therapy remains the most common method of stroke prevention in patients with atrial fibrillation. Time in therapeutic range (TTR) is a widely cited measure of the quality of VKA therapy. We sought to identify factors associated with TTR in a large, international clinical trial.

Methods and Results—TTR (international normalized ratio [INR] 2.0 to 3.0) was determined using standard linear interpolation in patients randomized to warfarin in the ROCKET AF trial. Factors associated with TTR at the individual patient level (i-TTR) were determined via multivariable linear regression. Among 6983 patients taking warfarin, recruited from 45 countries grouped into 7 regions, the mean i-TTR was 55.2% (SD 21.3%) and the median i-TTR was 57.9% (interquartile range 43.0% to 70.6%). The mean time with INR <2 was 29.1% and the mean time with an INR >3 was 15.7%. While multiple clinical features were associated with i-TTR, dominant determinants were previous warfarin use (mean i-TTR of 61.1% for warfarin-experienced versus 47.4% in VKA-naïve patients) and geographic region where patients were managed (mean i-TTR varied from 64.1% to 35.9%). These effects persisted in multivariable analysis. Regions with the lowest i-TTRs had INR distributions shifted toward lower INR values and had longer inter-INR test intervals.

Conclusions—Independent of patient clinical features, the regional location of medical care is a dominant determinant of variation in i-TTR in global studies of warfarin. Regional differences in mean i-TTR are heavily influenced by subtherapeutic INR values and are associated with reduced frequency of INR testing.

Clinical Trial Registration—URL: ClinicalTrials.gov. Unique identifier: NCT00403767. (***J Am Heart Assoc.*** **2013;2:e000067 doi: 10.1161/JAHA.112.000067**)

Key Words: anticoagulants • arrhythmia • embolism • prevention • risk factors

Table 3. Regional Mean i-TTR by Prior VKA Experience

	N	i-TTR, mean %	SE	Median (25th, 75th)	Parameter Estimate	*P* Value
VKA naïve						
East Asia	356	47.3	1.1	49 (34, 63)	−7.75	0.0005
India	87	32.6	2.5	29 (13, 49)	−22.46	<0.0001
Eastern Europe	1414	45.2	0.6	47 (31, 61)	−9.90	<0.0001
Western Europe/similar	233	57.8	1.3	62 (48, 72)	2.72	0.25
South Africa	29	46.5	4.8	47 (26, 64)	−8.57	0.054
Latin America	348	50.1	1.1	54 (37, 64)	−5.00	0.025
Canada/United States	129	55.1	1.8	58 (46, 70)	Ref	
VKA experienced but warfarin naïve*						
East Asia	0					
India	20	45.5	5.1	47 (28, 63)	−14.72	0.0006
Eastern Europe	619	53.6	0.8	55 (43, 68)	−6.53	<0.0001
Western Europe/similar	399	60.1	0.9	63 (50, 73)	Ref	
South Africa	0					
Latin America	293	60.1	1.0	62 (50, 72)	−0.08	0.96
Canada/United States	3	64.1	3.8	65 (57, 70)		
Warfarin experienced						
East Asia	371	53.3	1.1	56 (41, 68)	−11.83	<0.0001
India	23	39.9	4.6	42 (27, 52)	−25.25	<0.0001
Eastern Europe	630	55.9	0.7	58 (45, 70)	−9.16	<0.0001
Western Europe/similar	456	68.7	0.7	70 (60, 79)	3.61	0.64
South Africa	95	57.3	2.1	63 (46, 71)	−7.76	<0.0001
Latin America	283	56.4	1.2	59 (45, 71)	−8.75	<0.0001
Canada/United States	1195	65.1	0.5	67 (55, 78)	Ref	

Table 4. Regional Mean i-TTR After First 90 Days of Follow-up

Region	N	i-TTR, mean %	SD	Median (25th, 75th)	Parameter Estimate	*P* Value
East Asia	677	53.3	21.7	56 (40, 67)	−12.52	<0.0001
India	115	39.5	25.2	42 (21, 56)	−26.38	<0.0001
Eastern Europe	2462	53.0	21.5	55 (40, 68)	−12.82	<0.0001
Western Europe/similar	1019	66.6	17.7	69 (58, 79)	0.76	0.37
South Africa	115	57.6	21.1	59 (46, 74)	−8.19	<0.0001
Latin America	875	59.0	20.0	61 (48, 74)	−6.84	<0.0001
Canada/United States	1244	65.8	18.7	68 (56, 79)	Ref	

i-TTR indicates individual patient-level time in therapeutic range.

Variation in i-TTR Across Countries

There was substantial variation in i-TTR across the 45 countries in ROCKET AF, ranging from a mean of 36% to 75%. Substitution of individual countries for geographic regions in the multiple linear regression model led to an increase in the overall model R^2 from 16% to 19% (Table 6). Even within regions, there was considerable variability across countries (Figure 1). Of particular interest, the mean TTR was 47% in China and 38% in Taiwan but 66% in Hong Kong and 64% in Singapore. Ninety-nine percent of the patients in all 4 of these regions were identified as being of Asian race. When we substituted patient's race for patient's region in the multivariable model, the overall model R^2 deteriorated to 12.8% (Table 7).

and Western Europe/similar but 2.2 for patients in Eastern Europe and East Asia and 2.3 for patients in Latin America. The distributions were narrower in Canada/United States and Western Europe/similar with IQRs of 0.9 INR unit compared with East Asia and Latin America with IQRs of 1.0 INR unit and Eastern Europe with an IQR of 1.1 INR units (all $P<0.001$)

We compared the average number of days between INR measurements (Figure 3, Table 8). Patients in Canada/United States and Western Europe had the most frequent INR tests at an average interval of 19 and 20 days, respectively. By contrast, patients in Eastern Europe and in East Asia had the least frequent INR testing with an average interval of 23 days ($P<0.001$). We extended this analysis to compare the time to subsequent INR after an extreme INR value. There was marked variation in median time to a follow-up INR test after

Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients

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Summary

Atrial fibrillation (AF) carries an increased risk of ischaemic stroke, and oral anticoagulation with warfarin can reduce this risk. The objective of this study was to evaluate the association between time in therapeutic International Normalised Ratio (INR) range when receiving warfarin and the risk of stroke and mortality. The study cohort included AF patients aged 40 years and older included in the UK General Practice Research Database. For patients treated with warfarin we computed the percentage of follow-up time spent within therapeutic range. Cox regression was used to assess the association between INR and outcomes while controlling for patient demographics, health status and concomitant medication. The study population included 27,458 warfarin-treated (with at least 3 INR measurements) and 10,449 patients not treated with antithrombotic therapy. Overall the warfarin users spent 63% of their time within therapeutic range (TTR). This percentage did not vary substantially by age, sex and CHA_2DS_2-VASc score. Patients who spent at least 70% of time within therapeutic range had a 79% reduced risk of stroke compared to patients with ≤30% of time in range (adjusted relative rate of 0.21; 95% confidence interval 0.18–0.25). Mortality rates were also significantly lower with at least 70% of time spent within therapeutic range. In conclusion, good anticoagulation control was associated with a reduction in the risk of stroke.

Keywords

Atrial fibrillation, anticoagulation, stroke, treatment, warfarin

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users and 10,449 patients not treated with antithrombotic therapy. The median duration of follow-up was 1.7 years for warfarin users and 1.5 years for patients not treated with antithrombotic therapy (▶Table 1). The calendar year of the index dates ranged from 1991 to 2007. The majority of warfarin users (89.9%) was considered to be at high risk according to the CHA_2DS_2-VASc score (score ≥ 2). Patients using warfarin had on average a higher CHA_2DS_2-VASc score compared to patients not treated with antithrombotic therapy (in-

▶Figure 2 shows the Kaplan-Meier curves for time to stroke in the AF patients not treated with antithrombotic therapy and in warfarin users stratified by percentage of time spent within therapeutic range. Warfarin users with ≥ 70% of time spent within therapeutic range had the lowest risk of stroke while those with < 30% and 31–40% in range had the highest risks of stroke.

Sensitivity analyses showed similar results when restricting the data to the year 2000 or later (adjusted RR of 0.22 [95% confidence

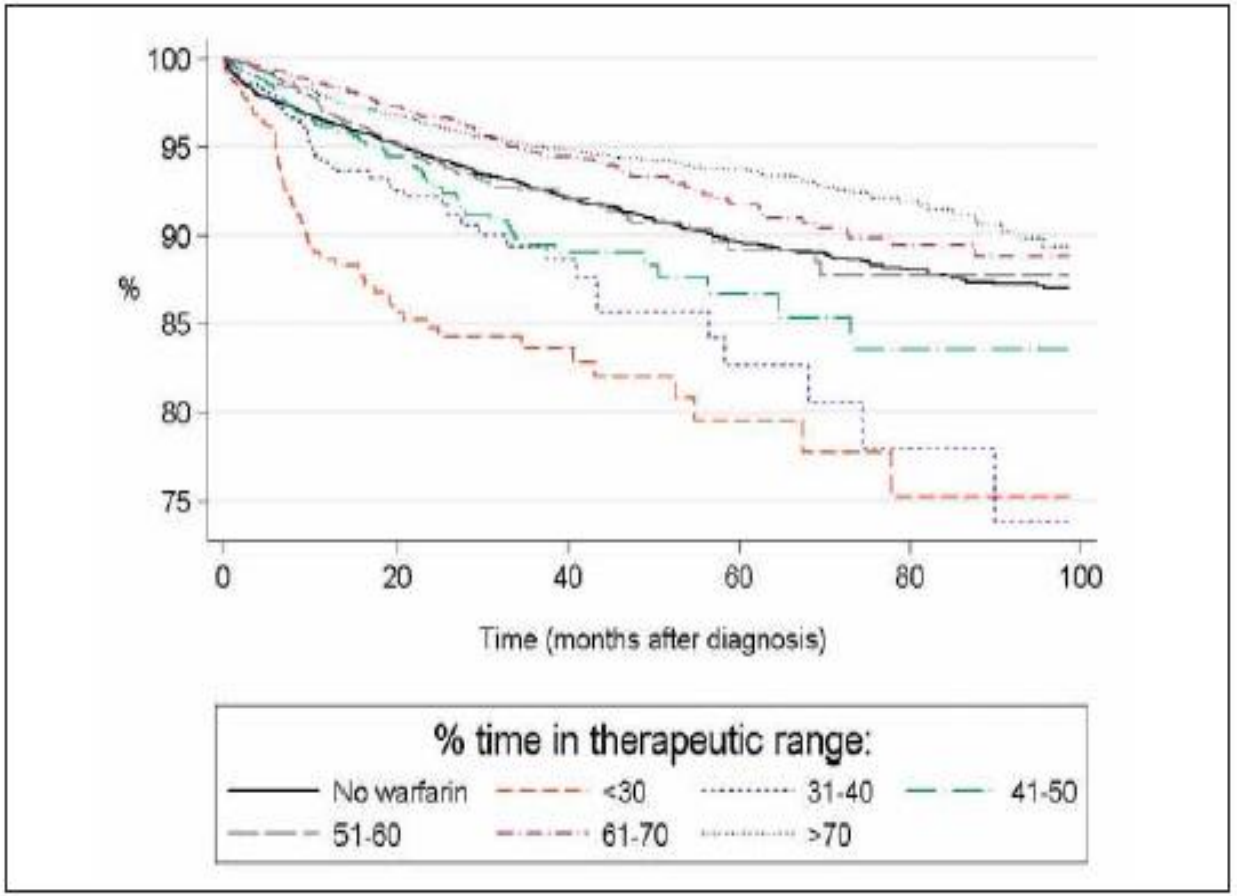

Figure 2: % of patients without a stroke over time stratified by time spent within therapeutic range (INR 2.0–3.0).

Benefit of Oral Anticoagulant Over Antiplatelet Therapy in Atrial Fibrillation Depends on the Quality of International Normalized Ratio Control Achieved by Centers and Countries as Measured by Time in Therapeutic Range

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Background—Oral anticoagulation (OAC) therapy is effective in atrial fibrillation but requires vigilance to maintain the international normalized ratio in the therapeutic range. This report examines how differences in time in therapeutic range (TTR) between centers and between countries affect the outcomes of OAC therapy.

Methods and Results—In a posthoc analysis, the TTRs of patients on OAC in a randomized trial of OAC versus clopidogrel plus aspirin (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events [ACTIVE W]) were used to calculate the mean TTR for each of 526 centers and 15 countries. Proportional-hazards analysis, with and without adjustment for baseline variables, was performed, with patients stratified by TTR quartile and country. A wide variation in TTRs was found between centers, with mean TTRs for centers in the 4 quartiles of 44%, 60%, 69%, and 78%. For patients at centers below the median TTR (65%), no treatment benefit was demonstrated as measured by relative risk for vascular events of clopidogrel plus aspirin versus OAC (relative risk, 0.93; 95% confidence interval, 0.70 to 1.24; $P=0.61$). However, for patients at centers with a TTR above the study median, OAC had a marked benefit, reducing vascular events by >2-fold (relative risk, 2.14; 95% confidence interval, 1.61 to 2.85; $P<0.0001$). Mean TTR also varied between countries from 46% to 78%; relative risk (clopidogrel plus aspirin versus OAC) varied from 0.6 to 3.6 (a 5-fold difference). A population-average model predicted that a TTR of 58% would be needed to be confident that patients would benefit from being on OAC.

Conclusions—A wide variation exists in international normalized ratio control, as measured by TTR, between clinical centers and between countries, which has a major impact on the treatment benefit of OAC therapy. For centers and countries, a target threshold TTR exists (estimated between 58% and 65%) below which there appears to be little benefit of OAC over antiplatelet therapy. (***Circulation*. 2008;118:2029-2037.**)

Table 1. TTR And Time to Risk of Stroke, Myocardial Infarction, Systemic Embolism, Vascular Death, or Major Hemorrhage for 15 Countries Participating in ACTIVE W

	Patients per TTR Quartile (Low to High), n					Clopidogrel+Aspirin		OAC		Clopidogrel+ASA vs OAC		
Country	1	2	3	4	Mean TTR	Events	%/y	Events	%/y	RR	95% CI	*P*
South Africa	55	43	0	0	46.3	5	8.42	8	14.94	0.57	0.19–1.75	0.33
Brazil	188	25	25	8	47.1	13	9.38	14	9.43	1.01	0.47–2.15	0.98
Russia	188	28	0	41	53.4	13	7.92	7	4.16	1.88	0.75–4.70	0.18
Poland	313	224	86	18	55.3	18	4.71	19	4.94	0.95	0.50–1.81	0.87
Belgium	4	128	9	0	58.7	11	11.91	6	6.72	1.81	0.67–4.90	0.24
United States	135	460	363	116	62.9	59	8.02	48	6.6	1.25	0.85–1.83	0.26
Netherlands	65	98	163	49	64.0	15	6.65	7	3.17	2.12	0.86–5.20	0.10
Argentina	40	79	76	106	64.5	10	6.02	10	5.9	1.03	0.43–2.48	0.94
Czech Republic	11	110	64	48	66.8	7	4.67	5	3.32	1.45	0.46–4.56	0.53
Italy	23	15	107	21	67.2	8	7.46	4	3.83	1.94	0.59–6.46	0.28
Canada	45	259	480	316	68.5	61	8.94	34	4.89	1.88	1.23–2.86	0.003
Germany	0	149	261	171	69.3	22	5.82	15	3.95	1.51	0.78–2.90	0.22
Australia	5	12	54	145	74.5	18	12.92	5	3.76	3.60	1.34–9.71	0.01
United Kingdom	2	34	59	199	74.8	12	7.03	7	3.97	1.79	0.71–4.55	0.22
Sweden	0	0	28	96	77.8	11	14.42	4	5.33	2.86	0.91–8.97	0.07

ASA indicates acetylsalicylic acid; RR, relative risk. Rows are ordered by mean TTR.

Table 3. Treatment Effects According to Center TTR Quartile: Risk Estimated by Time-to-Event Analysis

	Clopidogrel+ASA			OAC			Clopidogrel+ASA vs OAC			
	n	Events, n	%/y	n	Events, n	%/y	RR	95% CI	*P*	*P* for Interaction
Stroke, myocardial infarction, vascular death, or systemic embolism										
Quartile 1 (TTR <53.8%)	668	41	4.95	674	45	5.48	0.91	0.60–1.39	0.66	
Quartile 2 (TTR 53.8%–65.0%)	930	49	4.20	926	51	4.46	0.95	0.64–1.40	0.79	
Quartile 3 (TTR 65.1%–73.2%)	974	85	6.85	1004	39	3.04	2.29	1.57–3.35	<0.0001	
Quartile 4 (TTR >73.3%)	763	59	6.24	767	31	3.25	1.95	1.26–3.02	0.003	0.0008
Major hemorrhage										
Quartile 1 (TTR <53.8%)	668	12	1.45	674	24	2.92	0.49	0.25–0.99	0.046	
Quartile 2 (TTR 53.8%–65.0%)	930	22	1.89	926	27	2.36	0.79	0.45–1.40	0.42	
Quartile 3 (TTR 65.1%–73.2%)	974	42	3.38	1004	25	1.95	1.75	1.07–2.87	0.027	
Quartile 4 (TTR >73.3%)	763	25	2.64	767	17	1.78	1.48	0.80–2.75	0.21	0.013
Stroke, myocardial infarction, systemic embolism vascular death, or major hemorrhage										
Quartile 1 (TTR <53.8%)	668	53	6.40	674	59	7.18	0.89	0.62–1.29	0.55	
Quartile 2 (TTR 53.8%–65.0%)	930	70	6.00	926	70	6.13	0.98	0.71–1.37	0.92	
Quartile 3 (TTR 65.1%–73.2%)	974	113	9.10	1004	57	4.44	2.10	1.53–2.89	<0.0001	
Quartile 4 (TTR >73.3%)	763	80	8.46	767	44	4.62	1.87	1.30–2.71	0.0008	0.0003
Stroke										
Quartile 1 (TTR <53.8%)	668	18	2.17	674	16	1.95	1.12	0.57–2.20	0.74	
Quartile 2 (TTR 53.8%–65.0%)	930	19	1.63	926	14	1.23	1.33	0.67–2.66	0.41	
Quartile 3 (TTR 65.1%–73.2%)	974	38	3.06	1004	16	1.25	2.49	1.39–4.47	0.002	
Quartile 4 (TTR >73.3%)	763	25	2.64	767	13	1.36	1.95	1.00–3.82	0.05	0.2887
Stroke+Non-CNS systemic embolism										
Quartile 1 (TTR <53.8%)	668	20	2.42	674	16	1.95	1.25	0.65–2.41	0.51	
Quartile 2 (TTR 53.8%–65.0%)	930	25	2.14	926	14	1.23	1.76	0.91–3.39	0.09	
Quartile 3 (TTR 65.1%–73.2%)	974	44	3.54	1004	18	1.40	2.57	1.48–4.44	0.0008	
Quartile 4 (TTR >73.3%)	763	29	3.07	767	14	1.47	2.11	1.12–4.00	0.02	0.4034

CLINICAL PERSPECTIVE

Oral anticoagulation (OAC) has proved to be beneficial for the reduction of stroke and vascular events in atrial fibrillation. Previous studies have clearly shown that OAC therapy needs to be controlled carefully so that the international normalized ratio of the prothrombin time remains in the therapeutic range, between 2 and 3. However, this target is not always achieved. Previous studies have shown that the time in the therapeutic range (TTR) varies between patients and that a high TTR is associated with increased risk of stroke and bleeding. No previous study has indicated the minimum TTR needed to achieve a beneficial response from OAC. The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W) study data have been used to develop an estimate of the minimal TTR needed to confidently achieve a benefit compared with therapy with clopidogrel and aspirin. This estimate is based on comparing the outcomes of patients in ACTIVE W randomized to either OAC or clopidogrel plus aspirin. The analysis used stratification according to the TTR achieved by each clinical center in its OAC patients. Only patients at centers with TTR above the study median of 65% benefited from OAC compared with clopidogrel plus aspirin. An analysis by country has also been carried out, and a strong relationship has been found between the TTR achieved by a country and the benefit of OAC. The estimate of the minimum TTR needed to achieve a benefit from OAC therapy is between 58% and 65%. Centers that achieve below this level cannot be confident that their patients are benefiting from OAC compared with antiplatelet therapy. An even higher TTR (ie >70%) is associated with even greater benefit from OAC and was achieved in some countries. These data indicate that providers of OAC therapy need to evaluate how well they deliver OAC to patients with atrial fibrillation, with the intent of achieving a minimum TTR of 58% to 65% and an optimal control of >70% TTR.

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Apixaban versus Warfarin in Patients with Atrial Fibrillation

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MEAN TTR 62.2%

METHODS

In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

RESULTS

The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P<0.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; P=0.42).

CONCLUSIONS

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.)

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*The members of the steering committee, as well as other committee members and investigators in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, are listed in the Supplementary Appendix, available at NEJM.org.

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Table 2. Efficacy Outcomes.*

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

* Analyses were performed on data from the intention-to-treat population and included all events through the cutoff date for efficacy outcomes of January 30, 2011; comparisons of the primary outcome and of death from any cause were analyzed as part of hierarchical sequence testing (starting with testing the primary outcome for noninferiority, then the primary outcome for superiority, then major bleeding, and finally death from any cause), to control the type I error.

Table 3. Bleeding Outcomes and Net Clinical Outcomes.*

Outcome	Apixaban Group (N=9088)		Warfarin Group (N=9052)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary safety outcome: ISTH major bleeding†	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant nonmajor bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001
Net clinical outcomes						
Stroke, systemic embolism, or major bleeding	521	3.17	666	4.11	0.77 (0.69–0.86)	<0.001
Stroke, systemic embolism, major bleeding, or death from any cause	1009	6.13	1168	7.20	0.85 (0.78–0.92)	<0.001

* The bleeding outcomes were assessed in patients who received at least one dose of a study drug and events that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. The net clinical outcome includes all efficacy outcomes through the cutoff date for the efficacy analysis and bleeding outcomes that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. GUSTO denotes Global Use of Strategies to Open Occluded Coronary Arteries, and TIMI Thrombolysis in Myocardial Infarction.

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Edoxaban is a direct oral factor Xa inhibitor with proven antithrombotic effects. The long-term efficacy and safety of edoxaban as compared with warfarin in patients with atrial fibrillation is not known.

METHODS

We conducted a randomized, double-blind, double-dummy trial comparing two once-daily regimens of edoxaban with warfarin in 21,105 patients with moderate-to-high-risk atrial fibrillation (median follow-up, 2.8 years). The primary efficacy end point was stroke or systemic embolism. Each edoxaban regimen was tested for noninferiority to warfarin during the treatment period. The principal safety end point was major bleeding.

MEAN TTR 64.9%

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RESULTS

The annualized rate of the primary end point during treatment was 1.50% with warfarin (median time in the therapeutic range, 68.4%), as compared with 1.18% with high-dose edoxaban (hazard ratio, 0.79; 97.5% confidence interval [CI], 0.63 to 0.99; P<0.001 for noninferiority) and 1.61% with low-dose edoxaban (hazard ratio, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005 for noninferiority). In the intention-to-treat analysis, there was a trend favoring high-dose edoxaban versus warfarin (hazard ratio, 0.87; 97.5% CI, 0.73 to 1.04; P=0.08) and an unfavorable trend with low-dose edoxaban versus warfarin (hazard ratio, 1.13; 97.5% CI, 0.96 to 1.34; P=0.10). The annualized rate of major bleeding was 3.43% with warfarin versus 2.75% with high-dose edoxaban (hazard ratio, 0.80; 95% CI, 0.71 to 0.91; P<0.001) and 1.61% with low-dose edoxaban (hazard ratio, 0.47; 95% CI, 0.41 to 0.55; P<0.001). The corresponding annualized rates of death from cardiovascular causes were 3.17% versus 2.74% (hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.01), and 2.71% (hazard ratio, 0.85; 95% CI, 0.76 to 0.96; P=0.008), and the corresponding rates of the key secondary end point (a composite of stroke, systemic embolism, or death from cardiovascular causes) were 4.43% versus 3.85% (hazard ratio, 0.87; 95% CI, 0.78 to 0.96; P=0.005), and 4.23% (hazard ratio, 0.95; 95% CI, 0.86 to 1.05; P=0.32).

CONCLUSIONS

Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. (Funded by Daiichi Sankyo Pharma Development; ENGAGE AF-TIMI 48 ClinicalTrials.gov number, NCT00781391.)

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Table 3. Safety and Net Clinical End Points.*

Outcome	Warfarin (N=7012)		High-Dose Edoxaban (N=7012)		High-Dose Edoxaban vs. Warfarin		Low-Dose Edoxaban (N=7002)		Low-Dose Edoxaban vs. Warfarin	
					Hazard Ratio (95% CI)	P Value			Hazard Ratio (95% CI)	P Value
	no. of patients with event	*% of patients/yr*	*no. of patients with event*	*% of patients/yr*			*no. of patients with event*	*% of patients/yr*		
Major bleeding	524	3.43	418	2.75	0.80 (0.71–0.91)	<0.001	254	1.61	0.47 (0.41–0.55)	<0.001
Fatal	59	0.38	32	0.21	0.55 (0.36–0.84)	0.006	21	0.13	0.35 (0.21–0.57)	<0.001
Bleeding into a critical organ or area	211	1.36	108	0.70	0.51 (0.41–0.65)	<0.001	69	0.44	0.32 (0.24–0.42)	<0.001
Overt bleeding with blood loss of ≥2 g/dl	327	2.13	317	2.08	0.98 (0.84–1.14)	0.78	187	1.19	0.56 (0.47–0.67)	<0.001
Any intracranial bleeding	132	0.85	61	0.39	0.47 (0.34–0.63)	<0.001	41	0.26	0.30 (0.21–0.43)	<0.001
Fatal intracranial bleeding	42	0.27	24	0.15	0.58 (0.35–0.95)	0.03	12	0.08	0.28 (0.15–0.53)	<0.001
Gastrointestinal bleeding	190	1.23	232	1.51	1.23 (1.02–1.50)	0.03	129	0.82	0.67 (0.53–0.83)	<0.001
Upper gastrointestinal tract	111	0.71	140	0.91	1.27 (0.99–1.63)	0.06	88	0.56	0.78 (0.59–1.03)	0.08
Lower gastrointestinal tract	81	0.52	96	0.62	1.20 (0.89–1.61)	0.23	44	0.28	0.54 (0.37–0.77)	<0.001
Bleeding in other location	211	1.37	131	0.85	0.62 (0.50–0.78)	<0.001	87	0.55	0.40 (0.31–0.52)	<0.001
Bleeding during transition to open-label oral anticoagulation therapy										
Day 1–14	6	—	4	—	—	—	5	—	—	—
Day 15–30	5	—	6	—	—	—	13	—	—	—
Life-threatening bleeding	122	0.78	62	0.40	0.51 (0.38–0.70)	<0.001	40	0.25	0.32 (0.23–0.46)	<0.001
Clinically relevant nonmajor bleeding	1396	10.15	1214	8.67	0.86 (0.79–0.93)	<0.001	969	6.60	0.66 (0.60–0.71)	<0.001
Minor bleeding	714	4.89	604	4.12	0.84 (0.76–0.94)	0.002	533	3.52	0.72 (0.65–0.81)	<0.001
Major or clinically relevant nonmajor bleeding	1761	13.02	1528	11.10	0.86 (0.80–0.92)	<0.001	1161	7.97	0.62 (0.57–0.67)	<0.001
Any overt bleeding	2114	16.40	1865	14.15	0.87 (0.82–0.92)	<0.001	1499	10.68	0.66 (0.62–0.71)	<0.001
Net clinical outcome†										
Primary	1462	8.11	1323	7.26	0.89 (0.83–0.96)	0.003	1248	6.79	0.83 (0.77–0.90)	<0.001
Secondary	987	5.23	883	4.64	0.88 (0.81–0.97)	0.008	837	4.38	0.83 (0.76–0.91)	<0.001
Tertiary	1123	6.02	999	5.30	0.88 (0.81–0.96)	0.003	1010	5.37	0.89 (0.82–0.97)	0.007

Safety and efficacy of well managed warfarin

A report from the Swedish quality register Auricula

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Summary

The safety and efficacy of warfarin in a large, unselected cohort of warfarin-treated patients with high quality of care is comparable to that reported for non-vitamin K antagonists. Warfarin is commonly used for stroke prevention in atrial fibrillation, as well as for treatment and prevention of venous thromboembolism. While reducing risk of thrombotic/embolic incidents, warfarin increases the risk of bleeding. The aim of this study was to elucidate risks of bleeding and thromboembolism for patients on warfarin treatment in a large, unselected cohort with rigorously controlled treatment. This was a retrospective, registry-based study, covering all patients treated with warfarin in the Swedish national anticoagulation register Auricula, which records both primary and specialised care. The study included 77,423 unselected patients with 100,952 treatment periods of warfarin, constituting 217,804 treatment years. Study period was January 1, 2006 to December 31, 2011. Atrial fibrillation was the most common indication (68%). The mean time in therapeutic range of the international normalised ratio (INR) 2.0–3.0 was 76.5%. The annual incidence of severe bleeding was 2.24% and of thromboembolism 2.65%. The incidence of intracranial bleeding was 0.37% per treatment year in the whole population, and 0.38% among patients with atrial fibrillation. In conclusion, warfarin treatment where patients spend a high proportion of time in the therapeutic range is safe and effective, and will continue to be a valid treatment option in the era of newer oral anticoagulants.

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Table 3: Event rates in relation to gender and indication for treatment.

	Bleeding			Thrombosis		
	Intracranial	GI	Other	Stroke/TE/TIA	VTE	Myocardial infarction
All	0.37	0.73	1.16	1.38	0.28	1.05
	(0.36–0.38)	(0.71–0.75)	(1.14–1.19)	(1.36–1.41)	(0.27–0.29)	(1.02–1.07)
Men	0.39	0.72	1.04	1.34	0.25	1.09
	(0.38–0.41)	(0.70–0.75)	(1.01–1.07)	(1.31–1.38)	(0.24–0.27)	(1.06–1.12)
Women	0.34	0.73	1.31	1.36	0.31	0.94
	(0.32–0.36)	(0.71–0.76)	(1.27–1.35)	(1.32–1.40)	(0.29–0.33)	(0.91–0.97)
Atrial fibrillation	0.38	0.70	1.12	1.54	0.10	1.07
	(0.37–0.40)	(0.68–0.72)	(1.09–1.15)	(1.50–1.57)	(0.09–0.11)	(1.05–1.10)
Heart valve disease	0.51	1.11	1.83	1.48	0.03	1.12
	(0.46–0.55)	(1.04–1.18)	(1.74–1.91)	(1.40–1.56)	(0.02–0.05)	(1.06–1.19)
VTE	0.30	0.68	1.04	0.80	1.15	0.79
	(0.27–0.33)	(0.64–0.72)	(0.99–1.09)	(0.75–0.84)	(1.09–1.20)	(0.74–0.83)
Other indications	0.32	0.74	1.14	1.76	0.26	1.61
	(0.28–0.36)	(0.68–0.81)	(1.06–1.22)	(1.66–1.86)	(0.23–0.30)	(1.52–1.70)

TE, thromboembolism; TIA, transient ischaemic attack; VTE, venous thromboembolism.

	Age group					
	<50	50–60	60–70	70–80	80–90	>90
Bleeding						
Intracranial	0.12 (0.04–0.21)	0.24 (0.18–0.30)	0.28 (0.25–0.30)	0.39 (0.37–0.42)	0.45 (0.42–0.48)	0.83 (0.67–1.00)
Gastrointestinal	0.12 (0.04–0.21)	0.34 (0.27–0.41)	0.43 (0.39–0.47)	0.70 (0.66–0.73)	0.93 (0.88–0.97)	1.20 (1.00–1.40)
Other	0.49 (0.32–0.66)	0.73 (0.63–0.83)	0.76 (0.71–0.81)	0.99 (0.95–1.03)	1.55 (1.49–1.61)	2.13 (1.86–2.39)
Thrombosis						
Stroke/TE/TIA	0.44 (0.22–0.66)	0.13 (0.11–0.15)	1.31 (1.22–1.39)	1.71 (1.64–1.77)	2.28 (2.19–2.36)	2.56 (2.23–2.90)
Venous thromboembolism	0.12 (0.04–0.21)	0.07 (0.04–0.1)	0.08 (0.07–0.10)	0.10 (0.09–0.11)	0.12 (0.10–0.14)	-
Myocardial infarction	0.55 (0.30–0.79)	0.58 (0.46–0.70)	0.92 (0.85–0.99)	1.26 (1.21–1.32)	1.67 (1.60–1.74)	2.10 (1.80–2.39)

Table 4: Bleedings and thromboembolic events per treatment year in relation to age.

In AF, the net clinical benefit from anticoagulant treatment depends on the span in incidence rates of thromboembolic and bleeding events of comparable severity. In this study, all patients were on anticoagulant treatment and we therefore have no way of telling what the thromboembolic rate would have been if patients had not had treatment. In a previous study of 90,706 AF patients without anticoagulant treatment utilising the same Swedish registers as this study, the overall rate of strictly defined ischaemic stroke was 4.5%/year, of thromboembolism (including unspecified stroke, TIA and systemic embolism) 6.3%/year and of intracranial haemorrhage 0.6%/year (21). If structured and optimised care of warfarin patients can reduce bleeding rates to levels similar to that of untreated patients, few AF patients will not benefit from treatment. The lower the bleeding rates are, the higher the net benefit from treatment will be, if everything else remains unchanged. It has however to be kept in mind that the majority of those without anticoagulant treatment are elderly with high risk both of bleeding and thromboembolism (21). The risk of confounding by indication therefore makes it necessary to regard such comparisons with great care.

Patients with heart valve disease had more bleeding complications than other patients. Many of these patients had treatment with a higher therapeutic range of INR 2.5–3.5 instead of the more common of INR 2.0–3.0, which could account for some of those bleedings. We believe that it is important to report the actual risks these patients have of serious bleedings or thromboembolic events, not the least since the INR goals in many cases are founded on vague scientific evidence. The bias of including patients with higher INR goals than 2–3 means that, if anything, we show a larger risk of bleeding than for the patients with lower goals, and

Limitations

Since this is a retrospective registry-based study, we cannot exclude bias. However, the mere size of the cohort, and the fact that the Auricula data represent a nationwide Swedish cohort, both from anticoagulation clinics and primary health care settings, suggests that these results represent 'real world' clinical practice in Sweden. The positive predictive values for diagnoses in the Patient Register vary between diagnoses, but are generally in the range of 85–99% (22), although little is known about the negative predictive value for most diagnoses because this requires knowledge about true prevalence of diseases in the population, including subjects who have not yet received a diagnosis. Thus, registry studies are more prone to underestimating than to overestimating comorbidity.

What is known about this topic?

- Warfarin has a narrow therapeutic window, leading to an increased risk of complications when the treatment is poorly managed.
- NOACs have been shown to be safer than relatively poorly performed warfarin treatment, with TTR well under a recommended level of 70%.

What does this paper add?

- Efficient warfarin therapy with a mean TTR of 76.5% is possible to achieve in routine clinical care with unselected patients.
- Warfarin treatment with a high TTR performs well, and should not be ruled out in favour of NOACs.

Outcomes in a Warfarin-Treated Population With Atrial Fibrillation

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IMPORTANCE Vitamin K antagonist (eg, warfarin) use is nowadays challenged by the non–vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation (AF). NOAC studies were based on comparisons with warfarin arms with times in therapeutic range (TTRs) of 55.2% to 64.9%, making the results less credible in health care systems with higher TTRs.

OBJECTIVES To evaluate the efficacy and safety of well-managed warfarin therapy in patients with nonvalvular AF, the risk of complications, especially intracranial bleeding, in patients with concomitant use of aspirin, and the impact of international normalized ratio (INR) control.

DESIGN, SETTING, AND PARTICIPANTS A retrospective, multicenter cohort study based on Swedish registries, especially AuriculA, a quality register for AF and oral anticoagulation, was conducted. The register contains nationwide data, including that from specialized anticoagulation clinics and primary health care centers. A total of 40 449 patients starting warfarin therapy owing to nonvalvular AF during the study period were monitored until treatment cessation, death, or the end of the study. The study was conducted from January 1, 2006, to December 31, 2011, and data were analyzed between February 1 and November 15, 2015. Associating complications with risk factors and individual INR control, we evaluated the efficacy and safety of warfarin treatment in patients with concomitant aspirin therapy and those with no additional antiplatelet medications.

EXPOSURES Use of warfarin with and without concomitant therapy with aspirin.

MAIN OUTCOMES AND MEASURES Annual incidence of complications in association with individual TTR (iTTR), INR variability, and aspirin use and identification of factors indicating the probability of intracranial bleeding.

RESULTS Of the 40 449 patients included in the study, 16 201 (40.0%) were women; mean (SD) age of the cohort was 72.5 (10.1) years, and the mean CHA_2DS_2-VASc (cardiac failure or dysfunction, hypertension, age ≥75 years [doubled], diabetes mellitus, stroke [doubled]–vascular disease, age 65-74 years, and sex category [female]) score was 3.3 at baseline. The annual incidence, reported as percentage (95% CI) of all-cause mortality was 2.19% (2.07-2.31) and, for intracranial bleeding, 0.44% (0.39-0.49). Patients receiving concomitant aspirin had annual rates of any major bleeding of 3.07% (2.70-3.44) and thromboembolism of 4.90% (4.43-5.37), and those with renal failure were at higher risk of intracranial bleeding (hazard ratio, 2.25; 95% CI, 1.32-3.82). Annual rates of any major bleeding and any thromboembolism in iTTR less than 70% were 3.81% (3.51-4.11) and 4.41% (4.09-4.73), respectively, and, in high INR variability, were 3.04% (2.85-3.24) and 3.48% (3.27-3.69), respectively. For patients with iTTR 70% or greater, the level of INR variability did not alter event rates.

CONCLUSIONS AND RELEVANCE Well-managed warfarin therapy is associated with a low risk of complications and is still a valid alternative for prophylaxis of AF-associated stroke. Therapy should be closely monitored for patients with renal failure, concomitant aspirin use, and poor INR control.

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Table 3. Warfarin Treatment Complications in Relation to INR Control[a]

	iTTR				INR Variability			
	<70% (n = 16 703)		≥70% (n = 22 185)		High (n = 21 021)		Low (n = 19 428)	
Characteristic	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
All-cause mortality	752	4.35 (4.03-4.66)	602	1.29 (1.18-1.39)	923	2.94 (2.75-3.14)	510	1.50 (1.37-1.63)
Any major bleeding	659	3.81 (3.51-4.11)	752	1.61 (1.49-1.73)	955	3.04 (2.85-3.24)	502	1.47 (1.34-1.61)
Intracranial	124	0.72 (0.59-0.85)	157	0.34 (0.28-0.39)	160	0.51 (0.43-0.59)	128	0.38 (0.31-0.44)
Gastrointestinal tract	216	1.26 (1.09-1.43)	260	0.56 (0.49-0.63)	326	1.05 (0.93-1.16)	168	0.50 (0.42-0.57)
Other	368	2.17 (1.94-2.40)	395	0.85 (0.77-0.94)	550	1.79 (1.63-1.94)	241	0.71 (0.62-0.81)
Any thromboembolism	763	4.41 (4.09-4.73)	1 107	2.37 (2.23-2.51)	1 093	3.48 (3.27-3.69)	839	2.46 (2.29-2.63)
Arterial	425	2.52 (2.28-2.76)	645	1.41 (1.30-1.53)	605	1.98 (1.82-2.14)	502	1.51 (1.38-1.65)
Myocardial infarction	323	1.90 (1.69-2.11)	449	0.98 (0.88-1.07)	471	1.53 (1.39-1.67)	323	0.96 (0.85-1.07)
Venous	41	0.24 (0.16-0.31)	43	0.09 (0.06-0.12)	51	0.16 (0.12-0.21)	37	0.11 (0.07-0.14)

Abbreviations: INR, international normalized ratio; iTTR, individual time in therapeutic range.

[a] Results presented in total numbers during the study period and complication per treatment year. High INR variability indicates INR variability greater than or equal to mean INR variability; low INR variability indicates less than mean INR variability.

Comparison of the Short-Term Risk of Bleeding and Arterial Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban Versus Vitamin K Antagonists

A French Nationwide Propensity-Matched Cohort Study

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Background—The safety and effectiveness of non–vitamin K antagonist (VKA) oral anticoagulants, dabigatran or rivaroxaban, were compared with VKA in anticoagulant-naive patients with nonvalvular atrial fibrillation during the early phase of anticoagulant therapy.

Methods and Results—With the use of the French medico-administrative databases (SNIIRAM and PMSI), this nationwide cohort study included patients with nonvalvular atrial fibrillation who initiated dabigatran or rivaroxaban between July and November 2012 or VKA between July and November 2011. Patients presenting a contraindication to oral anticoagulants were excluded. Dabigatran and rivaroxaban new users were matched to VKA new users by the use of 1:2 matching on the propensity score. Patients were followed for up to 90 days until outcome, death, loss to follow-up, or December 31 of the inclusion year. Hazard ratios of hospitalizations for bleeding and arterial thromboembolic events were estimated in an intent-to-treat analysis using Cox regression models. The population was composed of 19713 VKA, 8443 dabigatran, and 4651 rivaroxaban new users. All dabigatran- and rivaroxaban-treated patients were matched to 16014 and 9301 VKA-treated patients, respectively. Among dabigatran-, rivaroxaban-, and their VKA-matched–treated patients, 55 and 122 and 31 and 68 bleeding events and 33 and 58 and 12 and 28 arterial thromboembolic events were observed during follow-up, respectively. After matching, no statistically significant difference in bleeding (hazard ratio, 0.88; 95% confidence interval, 0.64–1.21) or thromboembolic (hazard ratio, 1.10; 95% confidence interval, 0.72–1.69) risk was observed between dabigatran and VKA new users. Bleeding (hazard ratio, 0.98; 95% confidence interval, 0.64–1.51) and ischemic (hazard ratio, 0.93; 95% confidence interval, 0.47–1.85) risks were comparable between rivaroxaban and VKA new users.

Conclusions—In this propensity-matched cohort study, our findings suggest that physicians should exercise caution when initiating either non-VKA oral anticoagulants or VKA in patients with nonvalvular atrial fibrillation.
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Discussion

In this large-scale, nationwide cohort study, no significant differences were observed between NOAC (dabigatran or rivaroxaban) and VKA in terms of hospitalizations for bleeding or for arterial thromboembolic events during the early phase of anticoagulant therapy among new users with nv-AF. To our knowledge, this is the first study to assess the short-term benefit/risk balance of both dabigatran and rivaroxaban versus VKA using French medico-administrative databases, because previous studies were conducted on Danish and US Medicare data.[15–20] This study also provides insight into French pre-

CLINICAL PERSPECTIVES

The non–vitamin K antagonists (VKA) oral anticoagulants (NOACs), such as the direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban, have provided patients who have atrial fibrillation with a convenient, fixed-dose alternative to VKAs. Although NOACs might have some advantages over VKAs, some concerns have emerged about their safety. Few real-world data has been reported so far, and few studies have specifically focused on the early phase of therapy. However, early bleeding and thromboembolic risks have been observed to be significantly higher during the first 90 days of therapy in patients who have atrial fibrillation initiating warfarin. We therefore conducted a large postmarketing study using the French medicoadministrative databases to better investigate the short-term comparative effectiveness and safety of each specific agent of NOAC versus VKA. In this nationwide propensity-matched cohort study (8443 dabigatran- and 4651 rivaroxaban-treated patients matched with at least 1 VKA user), no significant difference between NOAC (dabigatran or rivaroxaban) and VKA was found in terms of hospitalizations for bleeding or for arterial thromboembolic events during the early phase of therapy among new users with nonvalvular atrial fibrillation. Physicians must therefore be as cautious when initiating NOACs as when initiating VKAs, particularly in view of the absence of a NOAC antidote and objective monitoring of the extent of anticoagulation. These results are consistent with those from the few observational studies published to date and offer clinicians a more comprehensive picture of the NOAC benefit-risk balance during the early phase of treatment.

1151); in the **ROCKET AF trial (Rivaroxaban versus Warfarin in atrial fibrillation)** the mean TTR was 55% and ICH were 0.50% per year in the rivaroxaban group and 0.70% per year in the warfarin group **(24) (NEJM 2011; 365 : 883-891)**; in the **RE-COVER study (Dabigatran versus Warfarin in the treatment of acute venous thromboembolism)** the mean TTR was 60% and ICH were 0 in the Dabigatran group (n=1273) and were 3 in the Warfarin group (n=1266) **(25) (NEJM 2009 vol. 361 pp. 2342-2352)**; in the **RE-MEDY study (Extended use of Dabigatran, Warfarin or Placebo in venous thromboembolism)** the median TTR was 65.3% (in this study the mean TTR is not cited) and ICH were 2 in the Dabigatran group (n=1430) and 4 in the warfarin group (n=1426) **(26) (NEJM 2013 vol. 368 pp. 709-718)**; in the **ARISTOTLE trial (Apixaban versus Warfarin in patients with atrial fibrillation)** the mean TTR was 62.2% and ICH were 0.24% per year in the Apixaban group and 0.47% per year in the Warfarin group **(27) (NEJM 2011 vol. 368 pp. 981-992)**; in the **RE-COVER II study (Treatment of acute venous thromboembolism with Dabigatran or Warfarin and pooled analysis)** the mean TTR was 57% and ICH were 2 in the Dabigatran group (n=1279) and 6 in the Warfarin group (n=1289) **(28) (Circulation 2014 vol. 129 pp. 764-772)**; in the **EINSTEIN DVT (Oral Rivaroxaban for symptomatic venous thromboembolism)** study the mean TTR was 57.7% and the number or percentage

of ICH were not cited **(29) (NEJM 2010 vol. 363 : 2499-2510)**; in the **EINSTEIN-PE study (Oral Rivaroxaban for the treatment of symptomatic pulmonary embolism)** the mean TTR was 62.7% and fatal ICH were 2 (<0.1% per year) in the Rivaroxaban group (n=2419) and 2 (<0.1% per year) in the standard therapy group (enoxaparin + VKA for 3, 6 or 12 months) (n=2413); nonfatal ICH were 1 (<0.1% per year) in the Rivaroxaban group and 10 (0.4% per year) in the standard therapy group **(30) (NEJM 2010 vol. 363 : 2499-2510)**; in the **AMPLIFY trial (Oral Apixaban for the treatment of acute venous thromboembolism)** the mean TTR was 61% and ICH were 3 (0.1% per year) in the Apixaban group and 6 (0.2% per year) in the Warfarin group **(31) (NEJM 2013 vol. 369 pp. 799-808)**; in the **Hokusai-VTE trial (Edoxaban versus Warfarin for the treatment of acute venous thromboembolism)** the mean TTR was 63.5% and fatal ICH were 0 in the Edoxaban group and 6 (0.1% per year) in the Warfarin group; nonfatal ICH were 5 (0.1% per year) in the Edoxaban group and 12 (0.3% per year) in the Warfarin group **(32) (NEJM 2013 vol. 369 : 1406-1415)**; in the **ENGAGE AF-TIMI 48 trial (Edoxaban versus Warfarin in patients with atrial fibrillation)** the mean TTR was 64.9% and ICH were 0.39% per year in the Edoxaban high-dose group (60 mg. die), 0.26% per year in the Edoxaban low-dose group (30 mg. die) and 0.85% per year in the Warfarin group. Of these ICH, 0.15% per year were fatal in the Edoxaban high-dose group, 0.08 were fatal in the Edoxaban low-dose group and 0.27% per year were fatal in the Warfarin group **(33) (NEJM 2013 vol. 369 pp. 2093-2104)**. As cited before, in all the studies in

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

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ABSTRACT

BACKGROUND

The direct oral thrombin inhibitor dabigatran has a predictable anticoagulant effect and may be an alternative therapy to warfarin for patients who have acute venous thromboembolism.

METHODS

In a randomized, double-blind, noninferiority trial involving patients with acute venous thromboembolism who were initially given parenteral anticoagulation therapy for a median of 9 days (interquartile range, 8 to 11), we compared oral dabigatran, administered at a dose of 150 mg twice daily, with warfarin that was dose-adjusted to achieve an international normalized ratio of 2.0 to 3.0. The primary outcome was the 6-month incidence of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths. Safety end points included bleeding events, acute coronary syndromes, other adverse events, and results of liver-function tests.

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RESULTS

A total of 30 of the 1274 patients randomly assigned to receive dabigatran (2.4%), as compared with 27 of the 1265 patients randomly assigned to warfarin (2.1%), had recurrent venous thromboembolism; the difference in risk was 0.4 percentage points (95% confidence interval [CI], −0.8 to 1.5; P<0.001 for the prespecified non-inferiority margin). The hazard ratio with dabigatran was 1.10 (95% CI, 0.65 to 1.84). Major bleeding episodes occurred in 20 patients assigned to dabigatran (1.6%) and in 24 patients assigned to warfarin (1.9%) (hazard ratio with dabigatran, 0.82; 95% CI, 0.45 to 1.48), and episodes of any bleeding were observed in 205 patients assigned to dabigatran (16.1%) and 277 patients assigned to warfarin (21.9%; hazard ratio with dabigatran, 0.71; 95% CI, 0.59 to 0.85). The numbers of deaths, acute coronary syndromes, and abnormal liver-function tests were similar in the two groups. Adverse events leading to discontinuation of the study drug occurred in 9.0% of patients assigned to dabigatran and in 6.8% of patients assigned to warfarin (P=0.05).

CONCLUSIONS

For the treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective as warfarin, has a safety profile that is similar to that of warfarin, and does not require laboratory monitoring. (ClinicalTrials.gov number, NCT00291330.)

MEAN TTR 60.0%

Table 2. Efficacy and Bleeding Outcomes.

Outcome	Dabigatran (N=1274)	Warfarin (N=1265)	Hazard Ratio (95% CI)*
Efficacy analysis†			
Primary end point of venous thromboembolism or related death — no. of subjects (%)			
During the study period	30 (2.4)	27 (2.1)	1.10 (0.65–1.84)
During the study period plus an additional 30-day follow-up‡	34 (2.7)	32 (2.5)	1.05 (0.65–1.70)
Secondary end point — no. of subjects (%)			
Symptomatic deep-vein thrombosis	16 (1.3)	18 (1.4)	0.87 (0.44–1.71)
Symptomatic nonfatal pulmonary embolism	13 (1.0)	7 (0.6)	1.85 (0.74–4.64)
Death related to venous thromboembolism	1 (0.1)	3 (0.2)	0.33 (0.03–3.15)
All deaths	21 (1.6)	21 (1.7)	0.98 (0.53–1.79)
Safety analysis§			
Major bleeding event — no. of subjects (%)	20 (1.6)	24 (1.9)	0.82 (0.45–1.48)
Fatal event — no. of events	1	1	
Bleeding into critical organ — no. of events	1	9	
Intracranial	0	3	
Hemarthrosis	1	5	
Hemoptysis	0	1	
Event resulting in fall in hemoglobin level or need for blood transfusions — no. of subjects (%)¶	20 (1.6)	18 (1.4)	
Major or clinically relevant nonmajor bleeding event — no. of subjects (%)	71 (5.6)	111 (8.8)	0.63 (0.47–0.84)

Treatment of Acute Venous Thromboembolism With Dabigatran or Warfarin and Pooled Analysis

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Background—Dabigatran and warfarin have been compared for the treatment of acute venous thromboembolism (VTE) in a previous trial. We undertook this study to extend those findings.

Methods and Results—In a randomized, double-blind, double-dummy trial of 2589 patients with acute VTE treated with low-molecular-weight or unfractionated heparin for 5 to 11 days, we compared dabigatran 150 mg twice daily with warfarin. The primary outcome, recurrent symptomatic, objectively confirmed VTE and related deaths during 6 months of treatment occurred in 30 of the 1279 dabigatran patients (2.3%) compared with 28 of the 1289 warfarin patients (2.2%; hazard ratio, 1.08; 95% confidence interval [CI], 0.64–1.80; absolute risk difference, 0.2%; 95% CI, −1.0 to 1.3; $P<0.001$ for the prespecified noninferiority margin for both criteria). The safety end point, major bleeding, occurred in 15 patients receiving dabigatran (1.2%) and in 22 receiving warfarin (1.7%; hazard ratio, 0.69; 95% CI, 0.36–1.32). Any bleeding occurred in 200 dabigatran (15.6%) and 285 warfarin (22.1%; hazard ratio, 0.67; 95% CI, 0.56–0.81) patients. Deaths, adverse events, and acute coronary syndromes were similar in both groups. Pooled analysis of this study RE-COVER II and the RE-COVER trial gave hazard ratios for recurrent VTE of 1.09 (95% CI, 0.76–1.57), for major bleeding of 0.73 (95% CI, 0.48–1.11), and for any bleeding of 0.70 (95% CI, 0.61–0.79).

Conclusion—Dabigatran has similar effects on VTE recurrence and a lower risk of bleeding compared with warfarin for the treatment of acute VTE.

Clinical Trial Registration—URL: www.clinicaltrials.gov. Unique identifiers: NCT00680186 and NCT00291330.

(*Circulation*. 2014;129:764-772.)

Table 1. Characteristics of the Patients and Treatments*

Characteristic	Dabigatran (n=1280)	Warfarin (n=1288)	*P* Value
Age, y	54.7±16.2	55.1±16.3	0.39
Median	56	57	
Range	18–92	18–93	
Female sex, n (%)	499 (39)	512 (39.8)	0.69
Race, n (%)†			1.00
White	993 (77.6)	999 (77.6)	
Black	19 (1.5)	19 (1.5)	
Asian	267 (20.9)	270 (21.0)	
Weight, kg	83.2±19.7	82.9±19.6	0.69
Median	80	81	
Range	36–184	35–210	
Body mass index, kg/m^2	28.4±5.8	28.4±5.8	0.89
Estimated creatinine clearance, mL/min‡	108.2±43.7	107.1±41.1	0.50
Type of index event, n (%)			0.85
Deep vein thrombosis only	877 (68.5)	873 (67.8)	
Pulmonary embolism only	298 (23.3)	297 (23.1)	
Both deep vein thrombosis and pulmonary embolism	104 (8.1)	117 (9.1)	
Neither deep vein thrombosis nor pulmonary embolism§	1 (0.1)	1 (0.1)	
Cancer at baseline, n (%)	50 (3.9)	50 (3.9)	0.98
Previous venous thromboembolism, n (%)	247 (19.3)	203 (15.8)	0.02
Concomitant use of acetylsalicylic acid, n (%)	130 (10.2)	112 (8.7)	0.20

MEAN TTR 56.9%

Efficacy analysis†			
Primary end point of venous thromboembolism or related death, n subjects (%)			
During 6 mo	30 (2.3)	28 (2.2)	1.08 (0.64–1.80)
During the study period plus an additional 30-d follow-up‡	34 (2.7)	30 (2.3)	1.13 (0.69–1.85)
Secondary end point, n subjects (%)			
Symptomatic deep vein thrombosis	25 (2.0)	17 (1.3)	1.48 (0.80–2.74)
Symptomatic nonfatal pulmonary embolism	7 (0.5)	13 (1.0)	0.54 (0.21–1.35)
Death related to pulmonary embolism	3 (0.2)§	0 (0.0)	
All deaths	25 (2.0)	25 (1.9)	0.98 (0.56–1.71)
Safety analysis‖			
Major bleeding event, n subjects (%)	15 (1.2)	22 (1.7)	0.69 (0.36–1.32)
Fatal event, n events	0	1 (0.1)	
Bleeding into critical organ, n events	6	4	
Intracranial	2	2	
Retroperitoneal	2	0	
Intra-articular	1	0	
Intramuscular	0	1	
Other	1	1	
Event resulting in fall in hemoglobin level or need for blood transfusions, n subjects (%)¶	13 (1.0)	19 (1.5)	
Major or clinically relevant nonmajor bleeding event, n subjects (%)	64 (5.0)	102 (7.9)	0.62 (0.45–0.84)
Any bleeding event, n subjects (%)	200 (15.6)	285 (22.1)	0.67 (0.56–0.81)
Sites of bleeding, n events#			
Intracranial	2	6	
Intraocular	5	14	
Retroperitoneal	3	1	
Intra-articular	3	0	
Pericardial	0	1	
Intramuscular	6	20	
Gastrointestinal	48	33	

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

ABSTRACT

BACKGROUND

Rivaroxaban, an oral factor Xa inhibitor, may provide a simple, fixed-dose regimen for treating acute deep-vein thrombosis (DVT) and for continued treatment, without the need for laboratory monitoring.

METHODS

We conducted an open-label, randomized, event-driven, noninferiority study that compared oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months in patients with acute, symptomatic DVT. In parallel, we carried out a double-blind, randomized, event-driven superiority study that compared rivaroxaban alone (20 mg once daily) with placebo for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism. The primary efficacy outcome for both studies was recurrent venous thromboembolism. The principal safety outcome was major bleeding or clinically relevant nonmajor bleeding in the initial-treatment study and major bleeding in the continued-treatment study.

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RESULTS

The study of rivaroxaban for acute DVT included 3449 patients: 1731 given rivaroxaban and 1718 given enoxaparin plus a vitamin K antagonist. Rivaroxaban had noninferior efficacy with respect to the primary outcome (36 events [2.1%], vs. 51 events with enoxaparin–vitamin K antagonist [3.0%]; hazard ratio, 0.68; 95% confidence interval [CI], 0.44 to 1.04; P<0.001). The principal safety outcome occurred in 8.1% of the patients in each group. In the continued-treatment study, which included 602 patients in the rivaroxaban group and 594 in the placebo group, rivaroxaban had superior efficacy (8 events [1.3%], vs. 42 with placebo [7.1%]; hazard ratio, 0.18; 95% CI, 0.09 to 0.39; P<0.001). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%), versus none in the placebo group (P=0.11).

CONCLUSIONS

Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation. (Funded by Bayer Schering Pharma and Ortho-McNeil; ClinicalTrials.gov numbers, NCT00440193 and NCT00439725.)

MEAN TTR 57.7%

*The investigators participating in the EINSTEIN–DVT and EINSTEIN–Extension Studies are listed in the Supplementary Appendix, available at NEJM.org.

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Table 1. Demographic and Clinical Characteristics of Patients with Deep-Vein Thrombosis, According to the Study and the Assigned Group.*

Characteristic	Acute DVT Study		Continued Treatment Study	
	Rivaroxaban (N=1731)	Standard Therapy† (N=1718)	Rivaroxaban (N=602)	Placebo (N=594)
Age — yr	55.8±16.4	56.4±16.3	58.2±15.6	58.4±16
Male sex — no. (%)	993 (57.4)	967 (56.3)	354 (58.8)	339 (57.1)
Weight — no. (%)				
≤50 kg	37 (2.1)	49 (2.9)	10 (1.7)	5 (0.8)
>50–100 kg	1443 (83.4)‡	1422 (82.8)‡	491 (81.6)‡	488 (82.2)‡
>100 kg	245 (14.2)‡	246 (14.3)‡	85 (14.1)‡	87 (14.6)‡
Missing data	6 (0.3)	1 (<0.1)	16 (2.7)	14 (2.4)
Creatinine clearance — no. (%)				
<30 ml/min	6 (0.3)	9 (0.5)	0	5 (0.8)
30–49 ml/min	115 (6.6)	120 (7.0)	37 (6.1)	44 (7.4)
50–79 ml/min	393 (22.7)	399 (23.2)	134 (22.3)	122 (20.5)
≥80 ml/min	1193 (68.9)	1170 (68.1)	373 (62.0)	373 (62.8)
Missing data	24 (1.4)	20 (1.2)	58 (9.6)	50 (8.4)
Initial diagnosis — no.				
DVT	1708	1697 (only 1 distal)	386	356
PE	12	11	216	238
Time from onset of symptoms to randomization — days				
Median	5	5	204	206

Table 3. Clinical Outcomes in the Acute DVT Study.*

Outcome	Rivaroxaban	Enoxaparin–VKA	Hazard Ratio (95% CI)	P Value
	no. (%)			
Efficacy				
Intention-to-treat population	1731	1718		
Recurrent VTE	36 (2.1)	51 (3.0)	0.68 (0.44–1.04)	<0.001†
Type of recurrent VTE				
Fatal PE	1	0		
PE could not be ruled out	3	6		
Nonfatal PE	20	18		
Recurrent DVT plus PE	1	0		
Recurrent DVT	14	28		
Net clinical benefit in terms of VTE plus major bleeding	51 (2.9)	73 (4.2)	0.67 (0.47–0.95)	0.03
Safety				
Safety population	1718	1711		
First major or clinically relevant nonmajor bleeding occurring during treatment	139 (8.1)	138 (8.1)	0.97 (0.76–1.22)	0.77
Major bleeding	14 (0.8)	20 (1.2)	0.65 (0.33–1.30)	0.21
Contributing to death	1 (<0.1)	5 (0.3)		
In a critical site	3 (0.2)	3 (0.2)		
Associated with a fall in hemoglobin of ≥2 g per deciliter, transfusion of ≥2 units, or both	10 (0.6)	12 (0.7)		
Clinically relevant nonmajor bleeding	126 (7.3)	119 (7.0)		
Total deaths through end of intended treatment period	38 (2.2)	49 (2.9)	0.67 (0.44–1.02)	0.06

Table 4. Clinical Outcomes in the Continued Treatment Study.*

Outcome	Rivaroxaban	Placebo	Hazard Ratio (95% CI)	P Value
	no. (%)			
Efficacy				
Intention-to-treat population	602	594		
Recurrent VTE	8 (1.3)	42 (7.1)†	0.18 (0.09–0.39)	<0.001
Type of recurrent VTE				
Fatal PE	0	1		
PE cannot be ruled out	1	0		
Nonfatal PE	2	13		
Recurrent DVT	5	31		
Safety				
Safety population	598	590		
First major or clinically relevant nonmajor bleeding	36 (6.0)	7 (1.2)	5.19 (2.3–11.7)	<0.001
Major bleeding†	4 (0.7)‡	0	NA	0.11
Contributing to death	0	0		
In a critical site	0	0		
Associated with a fall in hemoglobin of ≥2 g per deciliter, transfusion of ≥2 units, or both	4	0		
Clinically relevant nonmajor bleeding†	32 (5.4)‡	7 (1.2)		

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

The EINSTEIN–PE Investigators*

ABSTRACT

BACKGROUND

A fixed-dose regimen of rivaroxaban, an oral factor Xa inhibitor, has been shown to be as effective as standard anticoagulant therapy for the treatment of deep-vein thrombosis, without the need for laboratory monitoring. This approach may also simplify the treatment of pulmonary embolism.

METHODS

In a randomized, open-label, event-driven, noninferiority trial involving 4832 patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis, we compared rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist for 3, 6, or 12 months. The primary efficacy outcome was symptomatic recurrent venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding.

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RESULTS

Rivaroxaban was noninferior to standard therapy (noninferiority margin, 2.0; P=0.003) for the primary efficacy outcome, with 50 events in the rivaroxaban group (2.1%) versus 44 events in the standard-therapy group (1.8%) (hazard ratio, 1.12; 95% confidence interval [CI], 0.75 to 1.68). The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group (hazard ratio, 0.90; 95% CI, 0.76 to 1.07; P=0.23). Major bleeding was observed in 26 patients (1.1%) in the rivaroxaban group and 52 patients (2.2%) in the standard-therapy group (hazard ratio, 0.49; 95% CI, 0.31 to 0.79; P=0.003). Rates of other adverse events were similar in the two groups.

CONCLUSIONS

A fixed-dose regimen of rivaroxaban alone was noninferior to standard therapy for the initial and long-term treatment of pulmonary embolism and had a potentially improved benefit–risk profile. (Funded by Bayer HealthCare and Janssen Pharmaceuticals; EINSTEIN-PE ClinicalTrials.gov number, NCT00439777.)

MEAN TTR 62.7

The affiliations of the writing committee members are listed in the Appendix.

*The investigators participating in the EINSTEIN–Pulmonary Embolism (PE) Study and the study committees are listed in the Supplementary Appendix, available at NEJM.org.

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Table 3. Clinical Outcomes.

Outcome	Rivaroxaban	Standard Therapy	Hazard Ratio (95% CI)*	P Value
Efficacy				
Intention-to-treat population — no. of patients	2419	2413		
Recurrent venous thromboembolism — no. (%)	50 (2.1)	44 (1.8)	1.12 (0.75–1.68)	0.003†
Type of first recurrent venous thromboembolism — no.				
Fatal pulmonary embolism	2	1		
Death in which pulmonary embolism could not be ruled out	8	5		
Nonfatal pulmonary embolism	22	19		
Recurrent deep-vein thrombosis plus pulmonary embolism	0	2		
Recurrent deep-vein thrombosis	18	17		
Net clinical benefit: venous thromboembolism plus major bleeding — no. (%)‡	83 (3.4)	96 (4.0)	0.85 (0.63–1.14)	0.28

Safety				
No. of patients	2412	2405		
First episode of major or clinically relevant nonmajor bleeding during treatment — no. (%)	249 (10.3)	274 (11.4)	0.90 (0.76–1.07)	0.23
Major bleeding episode — no. (%)				
Any	26 (1.1)	52 (2.2)	0.49 (0.31–0.79)	0.003
Fatal	2 (<0.1)	3 (0.1)		
Retroperitoneal	0	1 (<0.1)		
Intracranial	2 (<0.1)	2 (<0.1)		
Other nonfatal episode in a critical site§	7 (0.3)	26 (1.1)		
Intracranial	1 (<0.1)	10 (0.4)		
Retroperitoneal	1 (<0.1)	7 (0.3)		
Intraocular	2 (<0.1)	2 (<0.1)		
Pericardial	0	2 (<0.1)		
Intraarticular	0	3 (0.1)		
Adrenal gland	1 (<0.1)	0		
Hemothorax	1 (<0.1)	1 (<0.1)		
Intraabdominal with hemodynamic instability	1 (<0.1)	2 (<0.1)		
Associated with a fall in hemoglobin of ≥2 g/dl, transfusion of ≥2 units, or both	17 (0.7)	26 (1.1)		

Table 3. (Continued.)

Outcome	Rivaroxaban	Standard Therapy	Hazard Ratio (95% CI)*	P Value
Clinically relevant nonmajor bleeding episode — no. (%)	228 (9.5)	235 (9.8)		
Death during intended treatment period — no. (%)	58 (2.4)	50 (2.1)	1.13 (0.77–1.65)	0.53
Cause of death — no.				
Pulmonary embolism or pulmonary embolism not ruled out¶	11	7		
Bleeding	5‖	4‖		
Cancer	20	23		
Myocardial infarction	2	1		
Ischemic stroke	2	1		
Other cardiac disorder or respiratory failure	4	4		
Infectious disease or septicemia	10	6		
Other	4	4		
Adverse event — no. (%)				
Any event emerging during treatment	1941 (80.5)	1903 (79.1)		0.24
Any serious event emerging during treatment	476 (19.7)	470 (19.5)		0.86
Any event resulting in permanent discontinuation of study drug	123 (5.1)	99 (4.1)		0.10
Any event leading to or prolonging hospitalization	475 (19.7)	430 (17.9)		0.82

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Oral Apixaban for the Treatment of Acute Venous Thromboembolism

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ABSTRACT

BACKGROUND

Apixaban, an oral factor Xa inhibitor administered in fixed doses, may simplify the treatment of venous thromboembolism.

METHODS

In this randomized, double-blind study, we compared apixaban (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) with conventional therapy (subcutaneous enoxaparin, followed by warfarin) in 5395 patients with acute venous thromboembolism. The primary efficacy outcome was recurrent symptomatic venous thromboembolism or death related to venous thromboembolism. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding.

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RESULTS

The primary efficacy outcome occurred in 59 of 2609 patients (2.3%) in the apixaban group, as compared with 71 of 2635 (2.7%) in the conventional-therapy group (relative risk, 0.84; 95% confidence interval [CI], 0.60 to 1.18; difference in risk [apixaban minus conventional therapy], −0.4 percentage points; 95% CI, −1.3 to 0.4). Apixaban was noninferior to conventional therapy ($P<0.001$) for predefined upper limits of the 95% confidence intervals for both relative risk (<1.80) and difference in risk (<3.5 percentage points). Major bleeding occurred in 0.6% of patients who received apixaban and in 1.8% of those who received conventional therapy (relative risk, 0.31; 95% CI, 0.17 to 0.55; $P<0.001$ for superiority). The composite outcome of major bleeding and clinically relevant nonmajor bleeding occurred in 4.3% of the patients in the apixaban group, as compared with 9.7% of those in the conventional-therapy group (relative risk, 0.44; 95% CI, 0.36 to 0.55; $P<0.001$). Rates of other adverse events were similar in the two groups.

CONCLUSIONS

A fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute venous thromboembolism and was associated with significantly less bleeding (Funded by Pfizer and Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00643201).

MEAN TTR 61.0%

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*Investigators in the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) trial are listed in the Supplementary Appendix, available at NEJM.org.

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Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Apixaban (N=2691)	Conventional Therapy (N=2704)
Age — yr	57.2±16.0	56.7±16.0
Male sex — no. (%)	1569 (58.3)	1598 (59.1)
Weight		
Mean — kg	84.6±19.8	84.6±19.8
Distribution — no. (%)		
≤60 kg	231 (8.6)	245 (9.1)
>60 to <100 kg	1932 (71.8)	1936 (71.6)
≥100 kg	522 (19.4)	518 (19.2)
Data missing	6 (0.2)	5 (0.2)
Creatinine clearance — no. (%)		
≤30 ml/min	14 (0.5)	15 (0.6)
>30 to ≤50 ml/min	161 (6.0)	148 (5.5)
>50 to ≤80 ml/min	549 (20.4)	544 (20.1)
>80 ml/min	1721 (64.0)	1757 (65.0)
Data missing	246 (9.1)	240 (8.9)
Qualifying diagnosis — no. (%)		
Deep-vein thrombosis	1749 (65.0)	1783 (65.9)
Pulmonary embolism	678 (25.2)	681 (25.2)
Pulmonary embolism with deep-vein thrombosis	252 (9.4)	225 (8.3)
Could not be evaluated	12 (0.4)	15 (0.6)

Table 1. (Continued.)

Characteristic	Apixaban (N=2691)	Conventional Therapy (N=2704)
Clinical presentation of VTE — no. (%)		
Unprovoked	2416 (89.8)	2429 (89.8)
Provoked	272 (10.1)	272 (10.1)
Not reported	3 (0.1)	3 (0.1)
Risk factors for recurrent VTE — no. (%)§		
Previous VTE	463 (17.2)	409 (15.1)
Known thrombophilia	74 (2.8)	59 (2.2)
Active cancer	66 (2.5)	77 (2.8)
Treatment with low-molecular-weight heparin, heparin, or fondaparinux before randomization — no. (%)		
None	358 (13.3)	381 (14.1)
≤12 hr	371 (13.8)	341 (12.6)
>12 to 24 hr	1116 (41.5)	1126 (41.6)
>24 to 36 hr	587 (21.8)	613 (22.7)
>36 to 48 hr	231 (8.6)	211 (7.8)
>48 hr	22 (0.8)	26 (1.0)
Data missing	6 (0.2)	6 (0.2)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. VTE denotes venous thromboembolism. There were no significant differences between the study groups in the baseline characteristics listed here.
† Patients may have undergone more than one imaging test.
‡ The anatomical extent of qualifying pulmonary embolism was defined as limited if it involved 25% or less of the vasculature of a single lobe, extensive if there were two or more lobes involving 50% or more of the vasculature for each lobe, and intermediate if neither of these definitions was met.
§ Patients could have had multiple risk factors or no additional risk factors.

Table 2. Clinical Outcomes during the Intended Treatment Period.*

Outcome	Apixaban (N=2691)	Conventional Therapy (N=2704)	Relative Risk (95% CI)	P Value
Efficacy				
No. of patients	2609	2635		
First recurrent VTE or VTE-related death — no. (%)	59 (2.3)	71 (2.7)	0.84 (0.60–1.18)	<0.001†
Type of first recurrent VTE — no. (%)				
Fatal PE	1 (<0.1)	2 (0.1)		
Death for which PE could not be ruled out	11 (0.4)	13 (0.5)		
Nonfatal PE with or without DVT	27 (1.0)	23 (0.9)		
DVT only	20 (0.8)	33 (1.3)		
Safety				
No. of patients	2676	2689		
Major bleeding — no. (%)‡	15 (0.6)	49 (1.8)	0.31 (0.17–0.55)	<0.001§
Fatal bleeding¶	1 (<0.1)	2 (0.1)		
Nonfatal major bleeding at a critical site	4 (0.1)	14 (0.5)		
Intracranial	3 (0.1)	6 (0.2)		
Retroperitoneal	1 (<0.1)	3 (0.1)		
Intrathoracic	0	1 (<0.1)		
Intraocular	0	2 (0.1)		
Intraarticular	0	2 (0.1)		
Other nonfatal major bleeding	10 (0.4)	33 (1.2)		
Gastrointestinal bleeding	7 (0.3)	18 (0.7)		
Intramuscular bleeding	0	5 (0.2)		
Epistaxis	1 (<0.1)	1 (<0.1)		
Urogenital bleeding	1 (<0.1)	3 (0.1)		
Subcutaneous hematoma	1 (<0.1)	6 (0.2)		

Table 2. (Continued.)

Outcome	Apixaban (N=2691)	Conventional Therapy (N=2704)	Relative Risk (95% CI)	P Value
Clinically relevant nonmajor bleeding — no. (%)	103 (3.8)	215 (8.0)	0.48 (0.38–0.60)	
Major bleeding or clinically relevant nonmajor bleeding — no. (%)‡	115 (4.3)	261 (9.7)	0.44 (0.36–0.55)	<0.001
Death during intended treatment period				
No. of patients/total no. (%)	41/2676 (1.5)	52/2689 (1.9)	0.79 (0.53–1.19)	
Cause of death — no./total no. (%)				
PE or PE not ruled out	12/2676 (0.4)	16/2689 (0.6)		
Cardiovascular cause	3/2676 (0.1)	7/2689 (0.3)		
Bleeding	2/2676 (0.1)	3/2689 (0.1)		
Cancer	14/2676 (0.5)	14/2689 (0.5)		
Infectious disease	9/2676 (0.3)	7/2689 (0.3)		
Other	1/2676 (<0.1)	5/2689 (0.2)		
Secondary composite outcomes				
VTE or death from cardiovascular cause — no./total no. (%)	61/2609 (2.3)	77/2635 (2.9)	0.80 (0.57–1.11)	0.18
VTE or death from any cause — no./total no. (%)	84/2609 (3.2)	104/2635 (3.9)	0.82 (0.61–1.08)	0.16
VTE, VTE-related death, or major bleeding — no./total no. (%)	73/2609 (2.8)	118/2635 (4.5)	0.62 (0.47–0.83)	0.001
Adverse events				
Any event during treatment — no./total no. (%)	1795/2676 (67.1)	1923/2689 (71.5)		
Any serious event during treatment — no./total no. (%)	417/2676 (15.6)	410/2689 (15.2)		
Any bleeding event — no./total no. (%)	415/2676 (15.5)	695/2689 (25.8)		
Any event resulting in permanent discontinuation of study drug — no./total no. (%)	162/2676 (6.1)	199/2689 (7.4)		

* DVT denotes deep-vein thrombosis, and PE pulmonary embolism.
† The P value is for noninferiority.
‡ For patients who had more than one event, only the first event was counted.
§ The P value is for superiority.
¶ Death from gastrointestinal bleeding occurred in one patient in each group, and death from intramuscular bleeding in one patient in the conventional-therapy group.

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Apixaban for Extended Treatment of Venous Thromboembolism

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ABSTRACT

BACKGROUND

Apixaban, an oral factor Xa inhibitor that can be administered in a simple, fixed-dose regimen, may be an option for the extended treatment of venous thromboembolism.

From the Department of Internal and Cardiovascular Medicine–Stroke Unit, University of Perugia, Perugia, Italy (G.A.);

METHODS

In this randomized, double-blind study, we compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy. The study drugs were administered for 12 months.

RESULTS

A total of 2486 patients underwent randomization, of whom 2482 were included in the intention-to-treat analyses. Symptomatic recurrent venous thromboembolism or death from venous thromboembolism occurred in 73 of the 829 patients (8.8%) who were receiving placebo, as compared with 14 of the 840 patients (1.7%) who were receiving 2.5 mg of apixaban (a difference of 7.2 percentage points; 95% confidence interval [CI], 5.0 to 9.3) and 14 of the 813 patients (1.7%) who were receiving 5 mg of apixaban (a difference of 7.0 percentage points; 95% CI, 4.9 to 9.1) ($P<0.001$ for both comparisons). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5-mg apixaban group, and 0.1% in the 5-mg apixaban group. The rates of clinically relevant nonmajor bleeding were 2.3% in the placebo group, 3.0% in the 2.5-mg apixaban group, and 4.2% in the 5-mg apixaban group. The rate of death from any cause was 1.7% in the placebo group, as compared with 0.8% in the 2.5-mg apixaban group and 0.5% in the 5-mg apixaban group.

CONCLUSIONS

Extended anticoagulation with apixaban at either a treatment dose (5 mg) or a thromboprophylactic dose (2.5 mg) reduced the risk of recurrent venous thromboembolism without increasing the rate of major bleeding. (Funded by Bristol-Myers Squibb and Pfizer; AMPLIFY-EXT ClinicalTrials.gov number, NCT00633893.)

ment of Vascular Medicine, Amsterdam (H.R.B.); King's College Hospital, London (A.C.); Pfizer, Groton, CT (M.C., M.J., A.P.); Flinders Medical Centre and Flinders University, Department of Haematology, Adelaide, SA, Australia (A.S.G.); the University of Oklahoma Health Sciences Center, College of Public Health, Oklahoma City (G.E.R.); and the Departments of Medicine and Biochemistry and Biomedical Sciences, McMaster University, and the Thrombosis and Atherosclerosis Research Institute — both in Hamilton, ON, Canada (J.I.W.). Address reprint requests to Dr. Agnelli at the University of Perugia, Piazzale Menghini 1, 06100 Perugia, Italy, or at agnellig@unipg.it.

*Additional investigators and committees for the Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy–Extended Treatment (AMPLIFY-EXT) study are listed in the Supplementary Appendix, available at NEJM.org.

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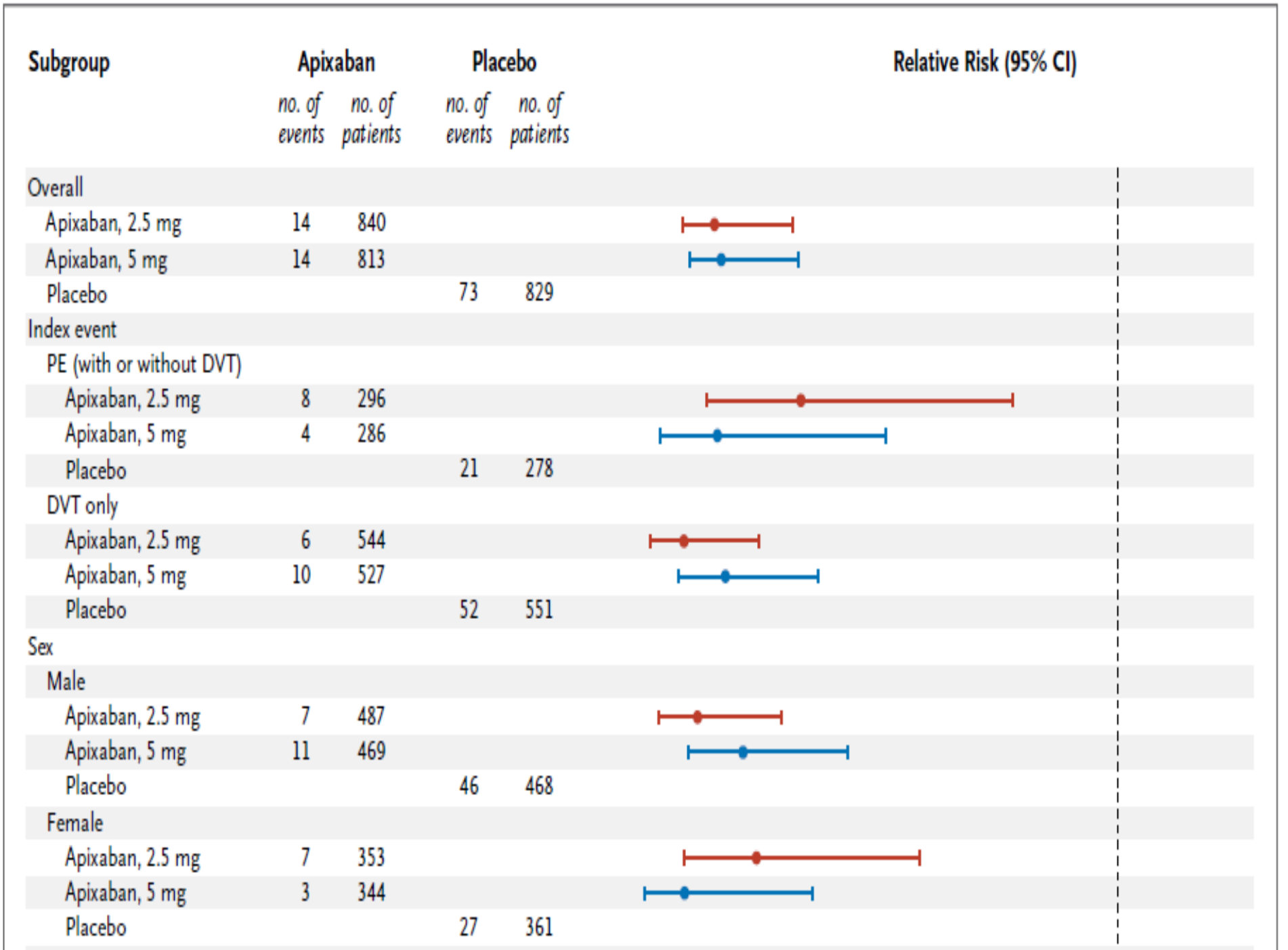
Table 2. Clinical Outcomes in the Intention-to-Treat Population during the Intended Active Study Period.*

Outcome	Apixaban, 2.5 mg (N=840)	Apixaban, 5 mg (N=813)	Placebo (N=829)	Relative Risk (95% CI)		
				Apixaban, 2.5 mg, vs. Placebo	Apixaban, 5 mg, vs. Placebo	Apixaban, 2.5 mg vs. 5 mg
	number (percent)					
Recurrent VTE or death from any cause — primary efficacy outcome†	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22–0.48)	0.36 (0.25–0.53)	NA
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11–0.33)	0.20 (0.11–0.34)	0.97 (0.46–2.02)
Non–VTE-related cardiovascular death, myocardial infarction, or stroke	4 (0.5)	5 (0.6)	11 (1.3)	0.36 (0.11–1.12)	0.47(0.16–1.33)	0.77 (0.21–2.88)
Recurrent VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease–related death	18 (2.1)	19 (2.3)	83 (10.0)	0.21 (0.13–0.35)	0.23 (0.14–0.38)	0.92 (0.48–1.74)
Major bleeding	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09–2.64)	0.25 (0.03–2.24)	1.93 (0.18–21.25)
Clinically relevant nonmajor bleeding	25 (3.0)	34 (4.2)	19 (2.3)	1.29 (0.72–2.33)	1.82 (1.05–3.18)	0.71 (0.43–1.18)
Major or clinically relevant nonmajor bleeding	27 (3.2)	35 (4.3)	22 (2.7)	1.20 (0.69–2.10)	1.62 (0.96–2.73)	0.74 (0.46–1.22)
VTE, VTE-related death, myocardial infarction, stroke, cardiovascular disease–related death, or major bleeding‡	20 (2.4)	20 (2.5)	86 (10.4)	0.23 (0.14–0.37)	0.24 (0.15–0.38)	0.97 (0.52–1.79)

* For patients who had more than one event, only the first event was considered. NA denotes not available.

† In the 2.5-mg apixaban group, 13 patients who were lost to follow-up were classified as having had a primary outcome event; in the 5-mg apixaban group, 20 patients who were lost to follow-up were classified as having had a primary outcome event; and in the placebo group, 19 patients who were lost to follow-up were classified as having had a primary outcome event.

‡ A reduction in this composite outcome was considered to represent the net clinical benefit.


Subgroup
Apixaban
Placebo
Relative Risk (95% CI)
no. of events
no. of patients
no. of events
no. of patients
Overall
Apixaban, 2.5 mg 14 840
Apixaban, 5 mg 14 813
Placebo 73 829
Index event
PE (with or without DVT)
Apixaban, 2.5 mg 8 296
Apixaban, 5 mg 4 286
Placebo 21 278
DVT only
Apixaban, 2.5 mg 6 544
Apixaban, 5 mg 10 527
Placebo 52 551
Sex
Male
Apixaban, 2.5 mg 7 487
Apixaban, 5 mg 11 469
Placebo 46 468
Female
Apixaban, 2.5 mg 7 353
Apixaban, 5 mg 3 344
Placebo 27 361

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

The Hokusai-VTE Investigators*

ABSTRACT

BACKGROUND

Whether the oral factor Xa inhibitor edoxaban can be an alternative to warfarin in patients with venous thromboembolism is unclear.

METHODS

In a randomized, double-blind, noninferiority study, we randomly assigned patients with acute venous thromboembolism, who had initially received heparin, to receive edoxaban at a dose of 60 mg once daily, or 30 mg once daily (e.g., in the case of patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg), or to receive warfarin. Patients received the study drug for 3 to 12 months. The primary efficacy outcome was recurrent symptomatic venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding.

The members of the writing committee (Harry R. Büller, M.D., Hervé Décousus, M.D., Michael A. Grosso, M.D., Michele Mercuri, M.D., Saskia Middeldorp, M.D., Martin H. Prins, M.D., Gary E. Raskob, Ph.D., Sebastian M. Schellong, M.D., Lee Schwocho, Ph.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Peter Verhamme, M.D., and Phil Wells, M.D.) assume responsibility for the content and integrity of the article. Address reprint requests to Dr. Büller at the Department of Vascular Medicine, Academic Medical Center, F4-275, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at h.r.buller@amc.uva.nl.

RESULTS

A total of 4921 patients presented with deep-vein thrombosis, and 3319 with a pulmonary embolism. Among patients receiving warfarin, the time in the therapeutic range was 63.5%. Edoxaban was noninferior to warfarin with respect to the primary efficacy outcome, which occurred in 130 patients in the edoxaban group (3.2%) and 146 patients in the warfarin group (3.5%) (hazard ratio, 0.89; 95% confidence interval [CI], 0.70 to 1.13; P<0.001 for noninferiority). The safety outcome occurred in 349 patients (8.5%) in the edoxaban group and 423 patients (10.3%) in the warfarin group (hazard ratio, 0.81; 95% CI, 0.71 to 0.94; P=0.004 for superiority). The rates of other adverse events were similar in the two groups. A total of 938 patients with pulmonary embolism had right ventricular dysfunction, as assessed by measurement of N-terminal pro–brain natriuretic peptide levels; the rate of recurrent venous thromboembolism in this subgroup was 3.3% in the edoxaban group and 6.2% in the warfarin group (hazard ratio, 0.52; 95% CI, 0.28 to 0.98).

CONCLUSIONS

Edoxaban administered once daily after initial treatment with heparin was noninferior to high-quality standard therapy and caused significantly less bleeding in a broad spectrum of patients with venous thromboembolism, including those with severe pulmonary embolism. (Funded by Daiichi-Sankyo; Hokusai-VTE ClinicalTrials.gov number, NCT00986154.)

MEAN TTR 63.5%

*The affiliations of the authors (members of the writing committee) are listed in the Appendix. The investigators participating in the Hokusai-VTE study and the study committees are listed in the Supplementary Appendix, available at NEJM.org.

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Table 2. Clinical Outcomes during Overall Study Period and On-Treatment Period.*

Outcome	Edoxaban (N=4118)	Warfarin (N=4122)	Hazard Ratio with Edoxaban (95% CI)	P Value
Primary efficacy outcome: first recurrent VTE or VTE-related death — no./total no. (%)				
All patients				
Event during overall study period	130/4118 (3.2)	146/4122 (3.5)	0.89 (0.70–1.13)	<0.001 (for noninferiority)
Fatal PE	4/4118 (0.1)	3/4122 (0.1)		
Death, with PE not ruled out	20/4118 (0.5)	21/4122 (0.5)		
Nonfatal PE with or without DVT	49/4118 (1.2)	59/4122 (1.4)		
DVT alone	57/4118 (1.4)	63/4122 (1.5)		
Event during on-treatment period	66/4118 (1.6)	80/4122 (1.9)	0.82 (0.60–1.14)	<0.001 (for noninferiority)
Patients with index DVT	2468/4188 (59.9)	2453/4122 (59.5)		
Event during overall study period	83/2468 (3.4)	81/2453 (3.3)	1.02 (0.75–1.38)	
Event during on-treatment period	48/2468 (1.9)	50/2453 (2.0)	0.96 (0.64–1.42)	
Patients with index PE	1650/4118 (40.1)	1669/4122 (40.5)		
Event during overall study period	47/1650 (2.8)	65/1669 (3.9)	0.73 (0.50–1.06)	
Event during on-treatment period	18/1650 (1.1)	30/1669 (1.8)	0.60 (0.34–1.08)	

Safety outcome during on-treatment period — no. (%)				
Primary safety outcome: first major or clinically relevant nonmajor bleeding	349 (8.5)	423 (10.3)	0.81 (0.71–0.94)	0.004 (for superiority)
Major bleeding	56 (1.4)	66 (1.6)	0.84 (0.59–1.21)	0.35 (for superiority)
Fatal	2 (<0.1)	10 (0.2)		
Intracranial	0	6 (0.1)		
Gastrointestinal	1 (<0.1)	2 (<0.1)		
Retroperitoneal	0	1 (<0.1)		
Other	1 (<0.1)	1 (<0.1)		
Nonfatal in critical site	13 (0.3)	25 (0.6)		
Intracranial	5 (0.1)	12 (0.3)		
Retroperitoneal	0	3 (0.1)		
Other	8 (0.2)	10 (0.2)		
Nonfatal in noncritical site	41 (1.0)	33 (0.8)		
Clinically relevant nonmajor bleeding	298 (7.2)	368 (8.9)	0.80 (0.68–0.93)	0.004 (for superiority)
Any bleeding	895 (21.7)	1056 (25.6)	0.82 (0.75–0.90)	<0.001 (for superiority)
Other adverse event — no. (%)				
Any adverse event occurring during on-treatment period	2821 (68.5)	2928 (71.0)		
Any serious adverse event	503 (12.2)	544 (13.2)		
Any serious adverse event leading to permanent discontinuation of the study drug	121 (2.9)	105 (2.5)		
Any drug-related adverse event leading to permanent discontinuation of the study drug	41 (1.0)	51 (1.2)		