Efficacy and Safety of Apixaban Compared With Warfarin at Different Levels of Predicted International Normalized Ratio Control for Stroke Prevention in Atrial Fibrillation

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Background—In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban compared with warfarin reduced stroke and systemic embolism, major bleeding, and mortality. We evaluated treatment effects in relation to 2 predictions of time in therapeutic range (TTR).

Methods and Results—The trial randomized 18 201 patients with atrial fibrillation to apixaban 5 mg twice daily or warfarin for at least 12 months. For each patient, a center average TTR was estimated with the use of a linear mixed model on the basis of the real TTRs in its warfarin-treated patients, with a fixed effect for country and random effect for center. For each patient, an individual TTR was also predicted with the use of a linear mixed effects model including patient characteristics as well. Median center average TTR was 66% (interquartile limits, 61% and 71%). Rates of stroke or systemic embolism, major bleeding, and mortality were consistently lower with apixaban than with warfarin across center average TTR and individual TTR quartiles. In the lowest and highest center average TTR quartiles, hazard ratios for stroke or systemic embolism were 0.73 (95% confidence interval [CI], 0.53–1.00) and 0.88 (95% CI, 0.57–1.35) ($P_{interaction}$=0.078), for mortality were 0.91 (95% CI, 0.74–1.13) and 0.91 (95% CI, 0.71–1.16) ($P_{interaction}$=0.34), and for major bleeding were 0.50 (95% CI, 0.36–0.70) and 0.75 (95% CI, 0.58–0.97) ($P_{interaction}$=0.095), respectively. Similar results were seen for quartiles of individual TTR.

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Conclusions—The benefits of apixaban compared with warfarin for stroke or systemic embolism, bleeding, and mortality appear similar across the range of centers' and patients' predicted quality of international normalized ratio control.

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Key Words: anticoagulation ■ apixaban ■ atrial fibrillation ■ bleeding ■ stroke ■ warfarin

Warfarin and other vitamin K antagonists effectively prevent stroke in patients with atrial fibrillation (AF), but they have a narrow therapeutic window with an increased risk of stroke and bleeding when above or below the therapeutic range of the international normalized ratio (INR) of 2.0 to 3.0.[1–3] The dose response is influenced by several factors such as age, body weight, genetic variation, food, and comedications. Regular INR-guided dose adjustments are therefore necessary.[1–3] However, there are large variations of the time in therapeutic range (TTR) across individuals, sites, and countries, and these variations are related to patient outcomes.[4–9] Several trials have shown recently that the quality of warfarin use, as measured with INR control at the center or country level, may interact with the treatment effects of new antithrombotic treatments when compared with warfarin.[10–12]

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Apixaban is a new oral direct factor Xa inhibitor providing stable anticoagulation at a fixed dose twice daily without the need for anticoagulation monitoring. In the prospective, randomized, and double-blind Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial including 18 201 patients with AF and at least 1 additional risk factor for stroke, apixaban 5 mg twice daily reduced stroke or systemic embolism, major bleeding, and mortality compared with warfarin with a median TTR of 66%.[13,14] On the basis of previous reports of interactions between treatment effects of novel antithrombotic strategies and the quality of INR control in the warfarin arm,[10–12] we evaluated the influence of participating centers' and patients' predicted quality of INR control on the effects of apixaban compared with warfarin on key clinical outcome events in this trial. Given the limited information available to a physician at the time of treatment selection, a prediction of INR integrating knowledge of the country and center performance in terms of INR control and the individual patient history will provide the best available means to identify those who will have better or worse outcomes on warfarin. Hence, the present study of treatment interactions with predicted TTR will determine whether such information is useful in the decision to prefer warfarin or apixaban in different patients or treatment settings.

Methods

Patients

The ARISTOTLE trial was a double-blind, double-dummy, randomized trial comparing apixaban 5 mg twice daily (or 2.5 mg twice daily for patients with at least 2 of the following 3 criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL [133 μmol/L]) with warfarin in patients with AF at risk for stroke. The design and main results have been published previously.[13,14] In brief, inclusion criteria were documented AF and ≥1 of the following risk factors for stroke: age ≥75 years; prior stroke, transient ischemic attack, or systemic embolism; symptomatic heart failure within 3 months or systolic dysfunction with a left ventricular ejection fraction ≤40%; diabetes mellitus; and hypertension requiring pharmacological treatment. Reasons for exclusion included AF due to a reversible cause; mitral stenosis; prosthetic heart valve or other indication for oral anticoagulation; need for aspirin in a dose >165 mg/d or in combination with clopidogrel; recent stroke (<7 days); increased risk of hemorrhage; anemia with hemoglobin <9 g/dL; creatinine clearance <25 mL/min; active liver disease; other comorbid condition with reduced life expectancy; and inability to comply with INR monitoring or other study procedures. Institutional review board approval and patient written informed consent were obtained before enrollment.

Randomization and Masking

Randomization was stratified by center and prior warfarin use status (naive or experienced, determined on the basis of whether warfarin or other vitamin K antagonists had been used previously for >30 consecutive days). Recruitment was monitored with the goal of including ≈40% warfarin-naive patients at all sites. Apixaban (or corresponding placebo) was supplied in tablets taken twice daily. Warfarin (or matching placebo) was provided as 2-mg tablets dosed by the investigator to achieve a target INR of 2.0 to 3.0. Patients who were taking vitamin K antagonists before randomization were instructed to discontinue the drug 3 days before randomization and were not dosed until the INR was <2.0. To maintain blinding, INRs were monitored with the use of an encrypted point-of-care INR device that provided a number to enter into the interactive voice recognition system that then presented the real INR for the patients on blinded warfarin or a sham INR for patients on warfarin placebo. During the titration phase, we recommended the use of a dosing algorithm with initial daily dose of up to 6 mg of warfarin (or warfarin placebo), unless the patient was previously on a stable dose of warfarin, in which case that dose might be resumed. Subsequent warfarin doses were recommended on the basis of an algorithm provided to the investigators; however, the final dose decision was left to the discretion of the investigator. INRs were monitored on day 4, twice a week for 2 weeks, once a week for 2 weeks, and monthly thereafter once a stable INR was obtained. Additional INR measurements were encouraged if clinically indicated. TTR was calculated by the method of Rosendaal.[15–17] A program seeking to improve the quality of INR control in the warfarin-treated patients included education, instructions, and feedback on INR control at the national and site levels. An algorithm was provided to manage temporary discontinuations in a blinded fashion.

Follow-Up and Clinical Outcomes

Patients were followed at monthly intervals after randomization and monthly thereafter until the study end. The primary efficacy outcome was stroke (ischemic, hemorrhagic, or unspecified) or systemic embolism. The primary safety outcome was International Society on Thrombosis and Hemostasis major bleeding. All-cause death was a key secondary outcome. Other predefined outcomes were the composites of stroke or systemic embolism and major bleeding and, as net clinical benefit, the composite of stroke or systemic embolism, all-cause death, and major bleeding. All primary and secondary efficacy and safety outcome events were adjudicated by a blinded clinical events committee using prespecified criteria and coordinated by the Duke Clinical Research Institute or Uppsala Clinical Research Center.

Statistical Analysis

The quality of INR control was quantified for all participating sites. First we calculated TTR for each individual warfarin-treated patient, during the entire treatment period, by the Rosendaal interpolation method.[15–17] We excluded INR levels during the first 7 days after randomization, during warfarin treatment interruptions, and beyond 2 days after the last dose of warfarin. Patients with <2 INR levels were excluded. Subsequently, each center's average TTR (cTTR) was estimated with the use of a linear mixed model for TTR in warfarin-treated patients, including a fixed effect for country and random effect for center. The TTR was transformed by a square root transformation to improve normality, and subjects were weighted according to the number of INR values that contributed to their TTR to reflect the greater variability that is likely to occur with fewer measurements. The cTTR was then predicted from the model with the use of empirical Bayes estimates of center effects and transformed back to the natural scale. The mixed model is designed to address the problem of measurement error, in which small sites will have greater variability in estimated TTR than large sites. The current approach is akin to regression calibration, a standard measurement error method. Thereafter, individual patient characteristics were added to the model and used to estimate individual patient–level predicted TTR (iTTR). Both models for TTR were fit on patients from the warfarin arm, and these models were used to obtain predictions for all patients based on their center (cTTR) and individual patient characteristics (iTTR). For both models, we report the likelihood ratio R^2 for mixed models.

In the analysis of outcome in relation to cTTR, the center's cTTR values were assigned to all patients representing the center's predicted quality of INR control during the trial. Similarly, iTTR was applied as an estimate of the individual quality of INR control that could be expected given a patient's center and baseline characteristics, regardless of study treatment. To address the primary hypothesis of effect modification according to predicted quality of INR control, we tested for an interaction between continuous cTTR or iTTR and treatment in a Cox regression model for outcome, including all patients. We did not assume linearity in testing this interaction but instead fitted a restricted cubic spline to cTTR and iTTR, respectively. In sensitivity analyses, we accounted for correlation between patients within the same center by using the empirical sandwich variance, and results were unchanged. The following outcomes were evaluated in these analyses: stroke or systemic embolism (primary efficacy outcome), major bleeding (primary safety outcome), total mortality, and the composite outcomes.

To simplify the description of patient characteristics and potential treatment interactions, centers (or patients) were then arranged in ascending quartiles of cTTR and iTTR. The interquartile cutoff limits were identified to keep the patient numbers within each quartile approximately balanced. Even when a statistically significant interaction was not present, the outcomes were presented across the 4 groups defined by the quartiles of cTTR and iTTR. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Baseline characteristics are compared across quartiles of predicted TTR with the use of the Kruskal-Wallis test for continuous variables and χ^2 tests for categorical variables. Continuous variables are presented as medians and 25th and 75th percentiles unless otherwise stated, and categorical variables are presented as counts and percentages. Two-sided α of 0.05 was used to determine statistical significance, although P values were not corrected for multiple testing.

Additional analyses were performed to describe the variability in INR across countries. In addition to the individual proportion of time in therapeutic range (iTTR), we calculated the individual proportions of time below range (INR <2) and time above range (INR >3). We described country INR control by calculating the median iTTR, time below range, and time above range among all warfarin-treated patients within a country and comparing these across countries.

These statistical analyses were performed at Duke Clinical Research Institute with the use of SAS software version 9.0 (SAS Institute, Inc, Cary, NC).

Results

The study randomized 18 201 patients from 1034 clinical centers in 39 countries. A total of 268 013 INR values corresponding to an average of 1.47 INR values per patient per month were collected during a median follow-up of 1.8 years.

Variation in TTR

The median (interquartile range) of TTR in the patients in the warfarin arm was 66.0% (52.4% to 76.5%). Countries exhibited substantial variation in INR control, with median TTR ranging from 46% to 80% (Figure 1). This was mainly driven by variability in the time below therapeutic range (INR <2.0), which ranged from 9% to 47%. Time above therapeutic range (INR >3.0) was more constant, with a range from 5% to 16% across countries. Variation was also observed between centers within a country, but the country differences were larger (Figure I in the online-only Data Supplement).

Predicted cTTR and iTTR

The median of predicted cTTR in the patients in the warfarin arm was 66.4%, with an interquartile range from 60.6% to 71.2%. The model for cTTR explained 29.6% (correlation coefficient 0.54) of the variability in iTTR. As expected, for iTTR there was a variability similar to that for cTTR among and within countries (Figure I in the online-only Data Supplement).

The median of predicted iTTR in the patients in the warfarin arm was 66.0%, with an interquartile range from 60.0% to 71.2%. In addition to center, the estimation of iTTR was based on the following characteristics related to iTTR in the warfarin group: country, age, sex, body weight, race, hypertension, smoking, diabetes mellitus, congestive heart failure, prior stroke, statin use, insulin use, vitamin K antagonist treatment experience, and amiodarone use. This model explained 29.9% of the variability in iTTR, which was only 0.3% more than that in the center-level model. The predictions of iTTR from this model had a correlation of 0.97 with cTTR (Figure II in the online-only Data Supplement).

Baseline Characteristics

When we compared the populations within the different quartiles of cTTR and iTTR, there were, as expected, several significant differences in baseline characteristics (Tables 1 and 2). However, because the randomization to the investigational treatment groups was stratified by center, these were well balanced between the treatment groups within each of the quartiles on the basis of cTTR or iTTR.

Clinical Outcomes in Relation to Predicted TTR

In the total population, the primary outcome of stroke or systemic embolism was 1.27% per year in the apixaban group and 1.60% per year in the warfarin group (HR=0.79 [95% CI, 0.66–0.95]). The treatment effect was maintained across different levels of predicted cTTR without any clear directional interaction, with HR=0.73 (95% CI, 0.53–1.00) in the lowest and HR=0.88 (95% CI, 0.57–1.35) (interaction with continuous cTTR, P=0.078) in the highest cTTR quartiles, respectively (Figures 2 and 3). The results were similar across different levels of predicted iTTR, with HR=0.70 (95% CI, 0.52–0.94) in the lowest and HR=0.87 (95% CI, 0.57–1.33) (interaction with continuous iTTR, P=0.060) in the highest iTTR quartiles, respectively

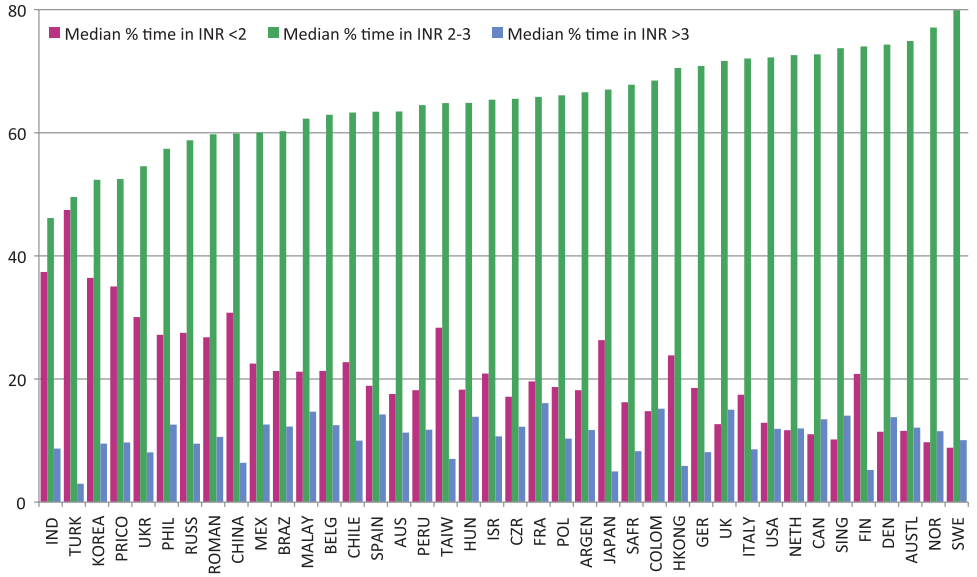

Figure 1. Country distribution of percentage of time in therapeutic range (TTR) of 2.0 to 3.0, percentage of time above treatment range (>3.0), and percentage of time below treatment range (<2.0) in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. ARGEN indicates Argentina; AUS, Austria; AUSTL, Australia; BELG, Belgium; BRAZ, Brazil; CAN, Canada; COLOM, Colombia; CZR, Czech Republic; DEN, Denmark; FIN, Finland; FRA, France; GER, Germany; HKONG, Hong Kong; HUN, Hungary; IND, India; INR, international normalized ratio; ISR, Israel; MALAY, Malaysia; MEX, Mexico; NETH, Netherlands; NOR, Norway; PHIL, Phillipines; POL, Poland; PRICO, Puerto Rico; ROMAN, Romania; RUSS, Russia; SAFR, South Africa; SING, Singapore; SWE, Sweden; TAIW, Taiwan; TURK, Turkey; and UKR, Ukraine.

(Figure 4). When the predicted TTR subgroups were further divided into patients with and without vitamin K antagonist treatment within 30 days of randomization, the results became more variable, probably because of chance due to low numbers of events in several subgroups (Tables I and II in the online-only Data Supplement).

In the overall study, total mortality was 3.52% per year with apixaban versus 3.94% per year with warfarin (HR=0.89 [95% CI, 0.80–0.99]). With regard to mortality, the treatment effect was identical in the lowest (HR=0.91 [95% CI, 0.74–1.13]) and highest (HR=0.91 [95% CI, 0.71–1.16]) cTTR quartiles (interaction with continuous cTTR, *P*=0.34) (Figures 2 and 3). The results were similar in relation to iTTR (Figure 4). These results were also consistent when the TTR subgroups were subdivided on the basis of previous vitamin K antagonist treatment (Tables I and II in the online-only Data Supplement).

In the overall study, major bleeding was substantially lower with apixaban (2.13% per year) than with warfarin (3.09% per year) (HR=0.69 [95% CI, 0.60–0.80]). There were substantial benefits of apixaban over warfarin across the range of cTTR, with HR for apixaban versus warfarin of 0.50 (95% CI, 0.36–0.70) in the lowest and 0.75 (95% CI, 0.58–0.97) in the highest cTTR quartiles (interaction with continuous cTTR, *P*=0.095) (Figures 2 and 3). The results were consistent in relation to iTTR, with HR=0.48 (95% CI, 0.35–0.67) in the lowest and 0.73 (95% CI, 0.55–0.94) in the highest iTTR quartiles (interaction with continuous iTTR, *P*=0.078) (Figure 4). These results were also consistent when the TTR subgroups were subdivided on the basis of previous vitamin K antagonist treatment (Tables I and II in the online-only Data Supplement).

We also analyzed the relations between the cTTR and iTTR quartiles, respectively, and the prespecified net clinical benefit (composite of stroke, systemic embolism, all-cause death, and major bleeding) and the composite of stroke, systemic embolism, and major bleeding. Regardless of cTTR or iTTR quartile, there were consistent benefits with apixaban compared with warfarin, with HR in the range of 0.61 to 0.92 and interaction *P* values between 0.32 and 0.85 (Figures 3 and 4). In addition, these results were consistent when the TTR subgroups were subdivided on the basis of previous vitamin K antagonist treatment (Tables I and II in the online-only Data Supplement).

Discussion

In the overall ARISTOTLE trial, apixaban, compared with warfarin, reduced the risk of stroke or systemic embolism, caused less major bleeding, and reduced mortality. The present complementary analyses showed that the reduction in the primary efficacy outcome of stroke or systemic embolism with apixaban was maintained across the broad range of centers' and patients' predicted quality of INR control. In addition, there was no significant interaction between the quality of INR control and the reduction of mortality. The reduction in major bleeding in patients receiving apixaban was also maintained regardless of centers' and patients' predicted TTR, although the magnitude of these benefits seemed to be attenuated in patients and centers with better expected INR control. When all major events were combined (ie, stroke, systemic embolism, all-cause death, and major bleeding), there was a consistent benefit with apixaban throughout the range of predicted TTR. These findings indicate similar benefits of apixaban versus warfarin for preventing stroke and reducing bleeding and all-cause mortality regardless of the expected quality of INR control with warfarin that can be achieved at different centers or for different patients.

Table 1. Baseline Characteristics in Relation to Quartiles of Predicted Centers' Time in Therapeutic Range

	Quartiles of Predicted Centers' TTR*				
	24.3–60.5	60.6–66.3	66.4–71.1	71.2–83.2	*P* Value
Patients randomized	n=4494	n=4553	n=4602	n=4552	
TTR in warfarin group					
No. (%)	2179 (48.5)	2224 (48.8)	2240 (48.7)	2226 (48.9)	
Median (Q1, Q3)	51.2 (35.6, 63.2)	62.6 (51.2, 72.4)	69.0 (58.4, 77.2)	76.6 (68.6, 83.5)	
Warfarin naive, No. (%)	2799 (62.3)	2259 (49.6)	1505 (32.7)	1237 (27.2)	<0.0001
Age, y, median (Q1, Q3)	68 (60, 74)	69 (62, 75)	71 (64, 77)	72 (66, 78)	<0.0001
Male, No. (%)	2711 (60.3)	2824 (62.0)	3039 (66.0)	3211 (70.5)	<0.0001
Weight, kg, median (Q1, Q3)	75.7 (64.0, 89.0)	80.0 (69.0, 93.0)	84.0 (71.6, 97.4)	88.1 (76.0, 102.1)	<0.0001
BP systolic, mm Hg, median (Q1, Q3)	130 (120, 140)	130 (120, 140)	130 (120, 141)	130 (120, 140)	0.0186
BP diastolic, mm Hg, median (Q1, Q3)	80 (74, 90)	80 (72, 88)	80 (70, 87)	79 (70, 85)	<0.0001
AF type, No. (%)					0.0049
Persistent or permanent	3822 (85.0)	3823 (84.0)	3849 (83.7)	3918 (86.1)	
Paroxysmal	672 (15.0)	729 (16.0)	752 (16.3)	633 (13.9)	
CHADS2 score, mean (SD)	2.2 (1.12)	2.1 (1.11)	2.1 (1.11)	2.0 (1.08)	<0.0001
CHADS2 category, No. (%)					<0.0001
0–1	1411 (31.4)	1528 (33.6)	1542 (33.5)	1702 (37.4)	
2	1612 (35.9)	1602 (35.2)	1660 (36.1)	1642 (36.1)	
3–6	1471 (32.7)	1423 (31.3)	1400 (30.4)	1208 (26.5)	
Age >75 y, No. (%)	842 (18.7)	1071 (23.5)	1403 (30.5)	1620 (35.6)	<0.0001
Previous stroke, No. (%)	619 (13.8)	572 (12.6)	543 (11.8)	393 (8.6)	<0.0001
Heart failure, No. (%)	1993 (44.3)	1615 (35.5)	1223 (26.6)	710 (15.6)	<0.0001
Diabetes mellitus, No. (%)	1074 (23.9)	1031 (22.6)	1157 (25.1)	1285 (28.2)	<0.0001
Hypertension, No. (%)	3886 (86.5)	4089 (89.8)	4047 (87.9)	3894 (85.5)	<0.0001
Previous MI, No. (%)	575 (12.8)	629 (13.8)	624 (13.6)	757 (16.6)	<0.0001
Baseline, No. (%)					
Aspirin	1440 (32.0)	1515 (33.3)	1386 (30.1)	1291 (28.4)	<0.0001
ARB	1011 (22.5)	1028 (22.6)	1112 (24.2)	1161 (25.5)	0.0014
ACEI/ARB	3117 (69.4)	3380 (74.2)	3239 (70.4)	3096 (68.0)	<0.0001
β-Blocker	2636 (58.7)	2821 (62.0)	2981 (64.8)	3044 (66.9)	<0.0001
Amiodarone	697 (15.5)	639 (14.0)	498 (10.8)	217 (4.8)	<0.0001
Digoxin	1657 (36.9)	1573 (34.5)	1311 (28.5)	1287 (28.3)	<0.0001
Lipid-lowering drug	1449 (32.2)	1622 (35.6)	2247 (48.8)	2881 (63.3)	<0.0001

ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; MI, myocardial infarction; and Q, quartile.

*Centers' time in therapeutic range (TTR) is defined in the Statistical Analysis section of Methods.

In this double-blind trial, the median TTR in the warfarin group was 66%. This overall standard of INR control seems better than in usual clinical practice, which often reports lower TTR.[18–21] However, in sites and countries with a more optimal anticoagulation service, even better results can be achieved.[22] The median TTR in ARISTOTLE was similar to that observed in several previous open-label warfarin controlled trials[10,11,23] and higher than that observed in a previous double-blind trial.[24] The comparison of TTR across trials is associated with several sources of bias, including standardization of INR measurements, blinding and completeness of reporting of INR results, frequency of INR monitoring, method for calculating TTR, and participating countries, sites, and population studied.

The variability in the quality of warfarin use has led to questions of how to interpret the overall findings for countries and sites with different standards of INR control.[11,12] In the absence of any indicator of anticoagulation status for patients in the apixaban group, the currently used models for evaluation of treatment effects in relation to statistically based predictions of TTR at trial entry represent further developments of previous methods to address this issue. In real-life healthcare situations, treatment decisions will be based on an integration of available information at the start of treatment. Therefore, a prediction of TTR seems to represent the best utilization of available information, at baseline, toward estimating outcomes while patients are on warfarin treatment. To this end, our first alternative was to base the prediction on the expected TTR in the center where the patient was randomized (ie, based on the average TTR each center achieved in its warfarin-treated patients during the trial [cTTR]). In this

Table 2. Baseline Characteristics in Relation to Quartiles of Predicted Individual Time in Therapeutic Range

	Quartiles of Predicted Individual TTR*				
	15.1–59.9	60.0–65.9	66.0–71.2	71.3–85.3	*P* Value
Patients randomized	n=4517	n=4496	n=4633	n=4555	
TTR in warfarin group					
No. (%)	2171 (48.1)	2205 (49.0)	2279 (49.2)	2213 (48.6)	
Median (Q1, Q3)	50.7 (34.0, 62.8)	62.3 (50.4, 71.9)	69.5 (59.4, 77.6)	76.6 (68.6, 83.5)	
Warfarin naive, No. (%)	3127 (69.2)	2329 (51.8)	1512 (32.6)	832 (18.3)	<0.0001
Age, y, median (Q1, Q3)	68 (59, 74)	70 (62, 75)	71 (64, 77)	71 (65, 77)	<0.0001
Male, No. (%)	2558 (56.6)	2732 (60.8)	3081 (66.5)	3414 (75.0)	<0.0001
Weight, kg, median (Q1, Q3)	75.0 (62.2, 89.9)	80.0 (69.0, 93.0)	83.9 (72.0, 97.0)	88.0 (76.9, 101.6)	<0.0001
BP systolic, mm Hg, median (Q1, Q3)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	0.0923
BP diastolic, mm Hg, median (Q1, Q3)	80 (72, 90)	80 (72, 88)	80 (70, 86)	80 (70, 85)	<0.0001
AF type, No. (%)					0.0787
Persistent or permanent	3811 (84.4)	3775 (84.0)	3916 (84.6)	3910 (85.8)	
Paroxysmal	706 (15.6)	720 (16.0)	715 (15.4)	645 (14.2)	
CHADS2 score, mean (SD)	2.3 (1.15)	2.2 (1.11)	2.1 (1.10)	1.9 (1.00)	<0.0001
CHADS2 category, No. (%)					<0.0001
0–1	1228 (27.2)	1416 (31.5)	1538 (33.2)	2001 (43.9)	
2	1631 (36.1)	1632 (36.3)	1669 (36.0)	1584 (34.8)	
3–6	1658 (36.7)	1448 (32.2)	1426 (30.8)	970 (21.3)	
Age >75 y, No. (%)	954 (21.1)	1119 (24.9)	1421 (30.7)	1442 (31.7)	<0.0001
Previous stroke, No. (%)	659 (14.6)	561 (12.5)	559 (12.1)	348 (7.6)	<0.0001
Heart failure, No. (%)	2216 (49.1)	1637 (36.4)	1187 (25.6)	501 (11.0)	<0.0001
Diabetes mellitus, No. (%)	1228 (27.2)	1130 (25.1)	1181 (25.5)	1008 (22.1)	<0.0001
Hypertension, No. (%)	3926 (86.9)	4012 (89.2)	4097 (88.4)	3881 (85.2)	<0.0001
Previous MI, No. (%)	615 (13.6)	590 (13.1)	695 (15.0)	685 (15.0)	0.0140
Baseline, No. (%)					
Aspirin	1560 (34.5)	1495 (33.3)	1401 (30.2)	1176 (25.8)	<0.0001
ACEI/ARB	3166 (70.1)	3353 (74.6)	3256 (70.3)	3057 (67.1)	<0.0001
β-Blocker	2630 (58.2)	2842 (63.2)	3007 (64.9)	3003 (65.9)	<0.0001
Amiodarone	869 (19.2)	648 (14.4)	389 (8.4)	145 (3.2)	<0.0001
Digoxin	1694 (37.5)	1487 (33.1)	1394 (30.1)	1253 (27.5)	<0.0001
Lipid-lowering drug	1387 (30.7)	1661 (36.9)	2297 (49.6)	2854 (62.7)	<0.0001

ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; MI, myocardial infarction; and Q, quartile.

*Individuals' time in therapeutic range (TTR) is defined in the Statistical Analysis section of Methods.

trial and other trials, the individual factors with the largest impact on INR control seemed to be the processes of care at the site and country levels, as shown by the wide variation in INR control among the countries and centers, which explained most of the variability in TTR between the patients. However, to better reflect the influence of individual patient factors, we also used a second model that included patient-related factors that influenced INR control during warfarin treatment, such as age, sex, body weight, smoking, diabetes mellitus, experience of vitamin K antagonist treatment, and concomitant amiodarone therapy (iTTR). By using these 2 approaches, we evaluated outcomes with apixaban versus warfarin in relation to all of the typically known information that a physician might use to estimate a patient's future quality of INR control when anticoagulant treatment is started. The similar results of these rigorous predictive models (cTTR and iTTR) strongly support the finding that the treatment effects with apixaban compared with warfarin are consistent across a broad range of predicted TTR levels at the start of treatment.

As in previous trials,[11,12] the differences in predicted TTRs were associated with differences in baseline characteristics, such as age, sex, body weight, heart failure, and warfarin experience, that contributed to differences in both TTR levels and outcomes. Thus, the observed differences in event rates across cTTR quartiles do not allow any causal interpretation because these differences were likely influenced by differences in socioeconomic status, healthcare systems, case mix, and medical treatments affecting both cTTR levels and outcomes. However, the comparisons between the randomized treatment groups within quartiles of cTTR and iTTR should be statistically valid because the randomization was stratified for center. On the basis of both models (cTTR

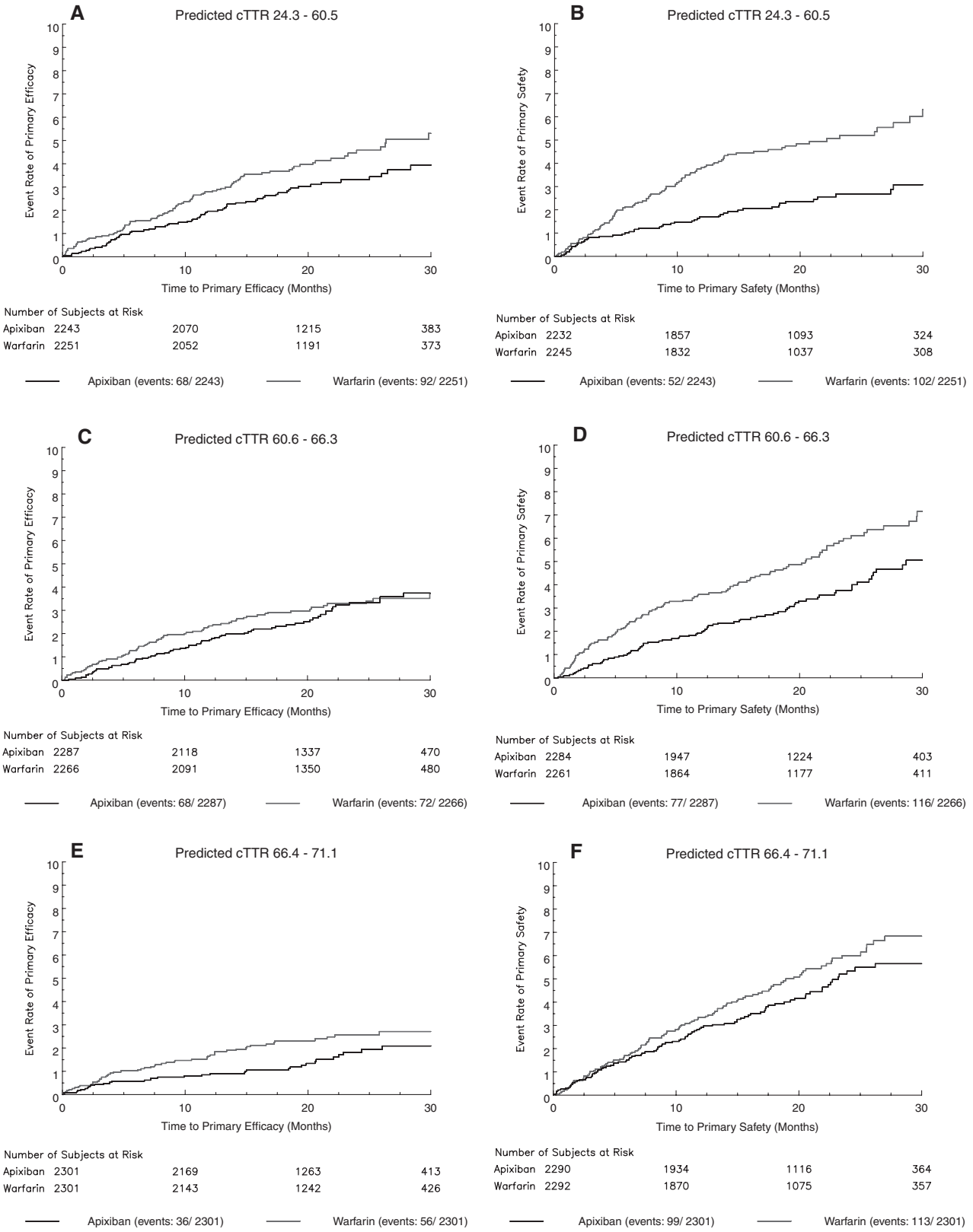

Figure 2. Cumulative risk of primary efficacy outcome (stroke or systemic embolism) in **A**, **C**, **E**, and **G** and primary safety outcome (major bleeding) in **B**, **D**, **F**, and **H** for apixaban compared with warfarin in relation to quartiles of predicted center-based international normalized ratio control (quartile 1: centers' time in therapeutic range [cTTR] ≤60.5%; quartile 2: cTTR 60.6–66.3%; quartile 3: cTTR 66.4–71.1%; quartile 4: cTTR ≥71.2%).

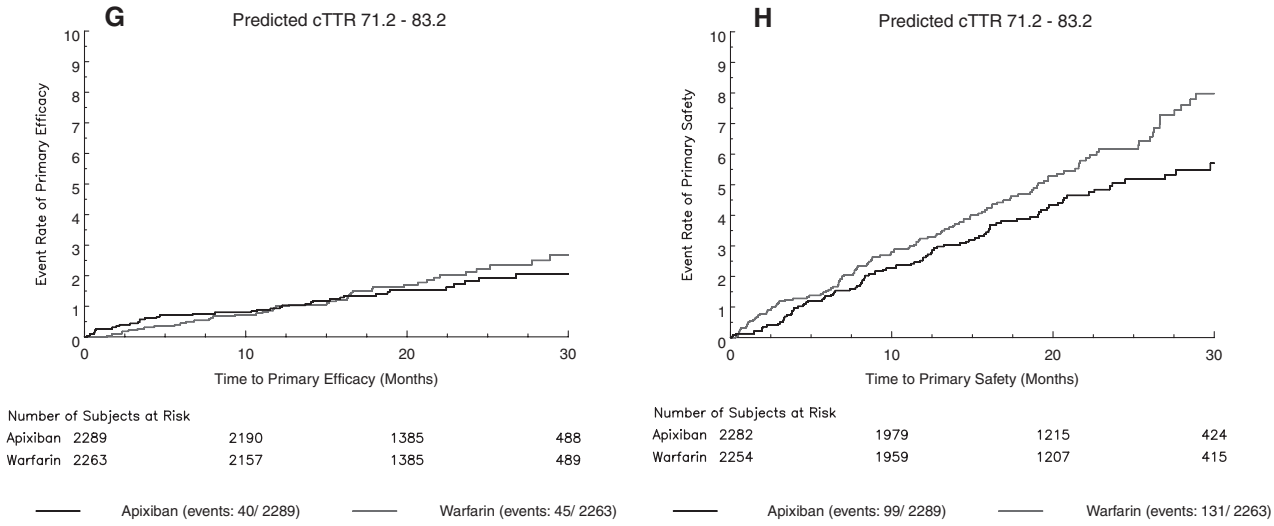

Figure 2. Continued

and iTTR), reductions in stroke or systemic embolism with apixaban compared with warfarin were maintained regardless of the predicted quality of INR control. Similar indications of persistent benefits have been seen with another new alternative agent to warfarin.[12] There was also a maintained advantage with apixaban over warfarin in terms of major bleeding across all center and patient characteristics that predicted levels of INR control. This is the first time that simultaneous benefits

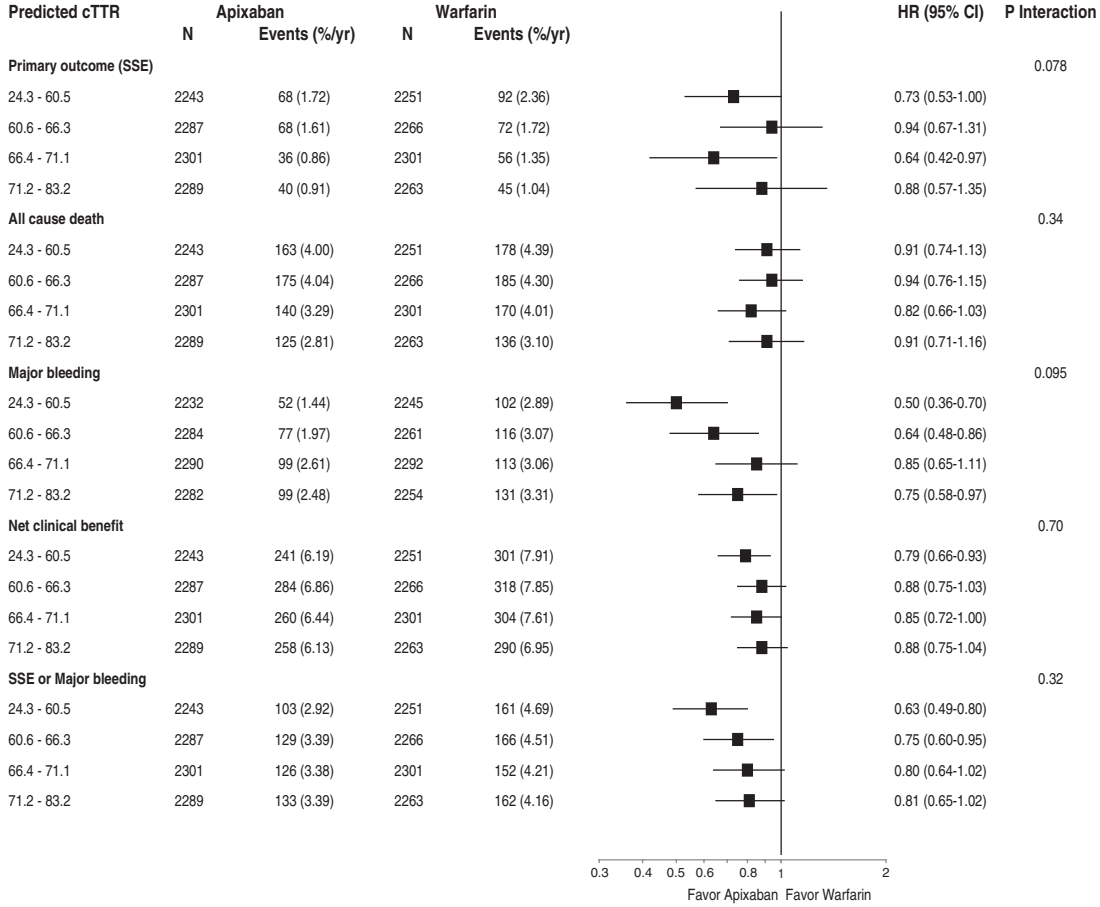

Figure 3. Outcome with apixaban vs warfarin in relation to quartiles of predicted centers' time in therapeutic range (cTTR). The interaction test was based on the continuous cTTR and restricted cubic spline for nonlinearity. The primary efficacy outcome was stroke (ischemic, hemorrhagic, or unspecified) or systemic embolism (SSE). Major bleeding was the primary safety outcome. Net clinical benefit was the composite of SSE, all-cause death, and major bleeding. CI indicates confidence interval; and HR, hazard ratio.

have been reported in the reduction of both stroke and bleeding events and in net clinical benefit by a novel agent versus warfarin regardless of the predicted quality of INR control.

These analyses have several limitations. Whereas the estimation of outcome in relation to cTTR was prespecified, the model in relation to iTTR was performed as a post hoc sensitivity analysis. The estimates of quality of INR control by cTTR and iTTR have the weakness of being based on post-randomization data. However, the predictions involved only baseline data that allowed groups to be defined and compared from the point of treatment initiation. As with all models, we are limited to studying measured covariates. Thus, our results are robust as long as we have collected the primary determinants of TTR that are regularly known at baseline. There are also relationships between both cTTR and iTTR and standards of care that make it difficult to draw conclusions regarding those factors that eventually might modulate the treatment effects. However, when one focuses on the question of whether centers or patients with better predicted INR control, through either favorable patients or better care or both, can expect similar results with apixaban compared with warfarin, as in the overall trial, it is not necessary to determine causal mechanisms. Finally, despite lack of statistical significance, there are trends toward attenuation of the treatment effects at centers and in patients with predicted excellent INR control in which interaction tests are less reliable because of low numbers of events and therefore lack of statistical power.

Conclusions

The benefits of apixaban over warfarin in preventing stroke, reducing all types of bleeding, and improving survival appear to be maintained regardless of centers' and patients' predicted quality of INR control. Therefore, in patients with AF and at least 1 additional risk factor for stroke, apixaban seems to be a more effective and safer treatment than warfarin across a broad range of quality of warfarin management.

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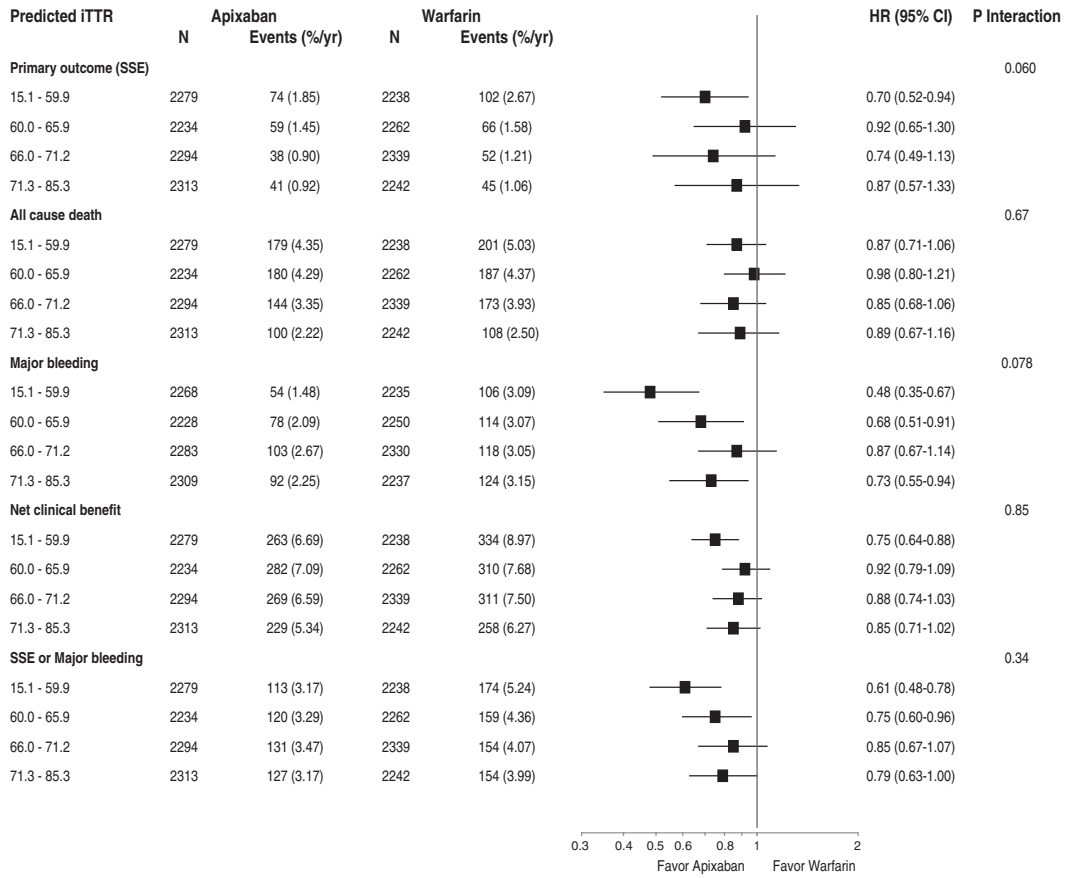

Figure 4. Outcome with apixaban vs warfarin in relation to quartiles of predicted individual time in therapeutic range (iTTR). The interaction test was based on the continuous iTTR. The primary efficacy outcome was stroke (ischemic, hemorrhagic, or unspecified) or systemic embolism (SSE). Major bleeding was the primary safety outcome. Net clinical benefit was the composite of SSE, all-cause death, and major bleeding. CI indicates confidence interval; and HR, hazard ratio.

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CLINICAL PERSPECTIVE

Warfarin effectively prevents stroke in patients with atrial fibrillation but has a narrow therapeutic window with an increased risk of stroke and bleeding when above or below the time in therapeutic range (TTR) of international normalized ratio of 2.0 to 3.0. There are large variations of TTR across individuals, sites, and countries, which are related to patient outcomes. The global Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial randomized 18 201 patients with atrial fibrillation in 1034 centers in 39 countries to apixaban or warfarin at a median TTR of 66% but with substantial variation between countries, centers, and patients. The overall results showed that apixaban reduced stroke by 21%, death by 11%, and major bleeding by 31%. Key additional questions involved the extent of benefits that remained in centers with higher TTR. The challenge in determining this issue is the lack of a comparable measure of the level of anticoagulation in both the apixaban and warfarin arms. We developed a new method in which, for each patient, a center average TTR was estimated with the use of a linear mixed model based on real TTRs in the warfarin-treated patients, with a fixed effect for country and random effect for center. For each patient, an individual TTR was also predicted with the use of a linear mixed effects model including patient characteristics as well. The results of these analyses consistently showed that the benefits of apixaban compared with warfarin for stroke or systemic embolism, bleeding, and mortality appeared similar across the range of centers' and patients' predicted quality of international normalized ratio control.

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Efficacy and Safety of Apixaban Compared With Warfarin at Different Levels of Predicted International Normalized Ratio Control for Stroke Prevention in Atrial Fibrillation

Lars Wallentin, Renato D. Lopes, Michael Hanna, Laine Thomas, Anne Hellkamp, Sunil Nepal, Elaine M. Hylek, Sana M. Al-Khatib, John H. Alexander, Marco Alings, John Amerena, Jack Ansell, Philip Aylward, Jozef Bartunek, Patrick Commerford, Raffaele De Caterina, Cetin Erol, Veli-Pekka Harjola, Claes Held, John D. Horowitz, Kurt Huber, Steen Husted, Matyas Keltai, Fernando Lanas, Liu Lisheng, John J.V. McMurray, Byung-Hee Oh, Mårten Rosenqvist, Witold Ruzyllo, Philippe Gabriel Steg, Dragos Vinereanu, Denis Xavier and Christopher B. Granger on behalf of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Investigators

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Supplemental Material

Efficacy and Safety of Apixaban Compared with Warfarin at Different Levels of Predicted INR Control for Stroke Prevention in Atrial Fibrillation

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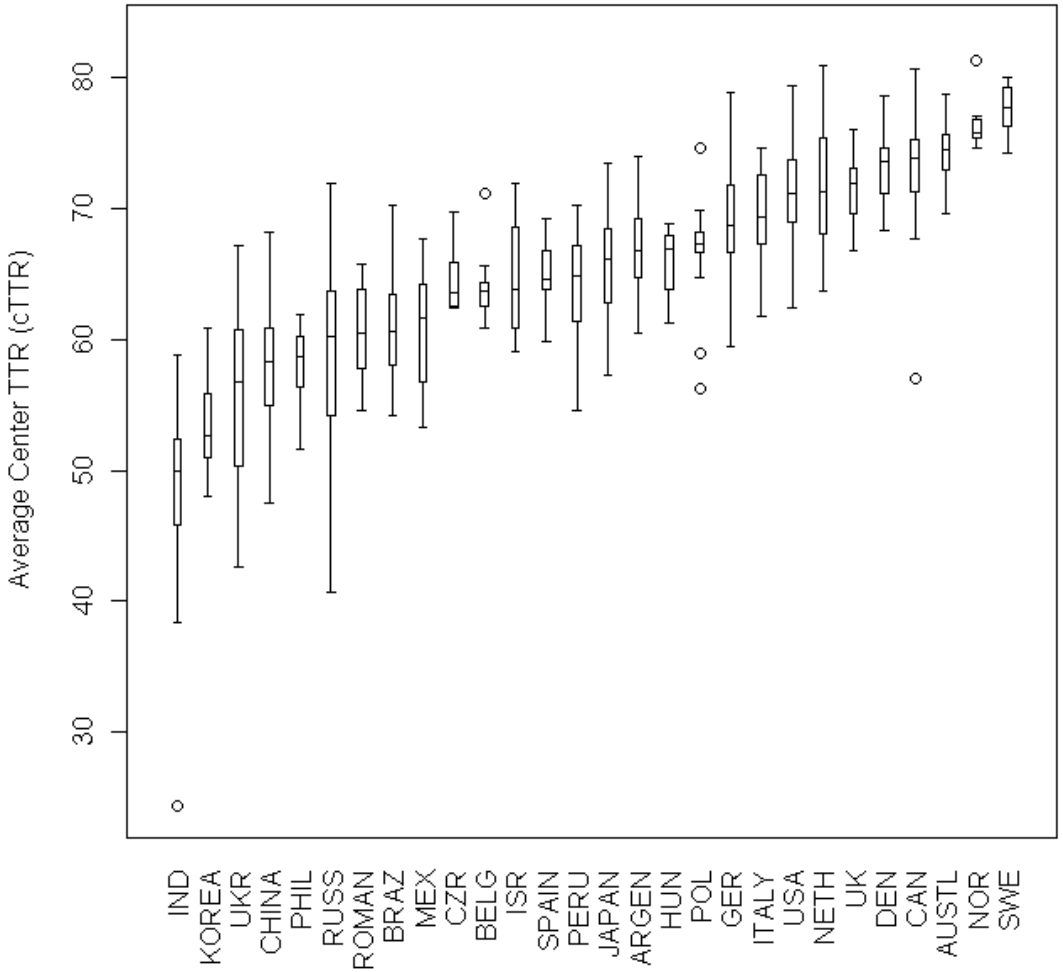
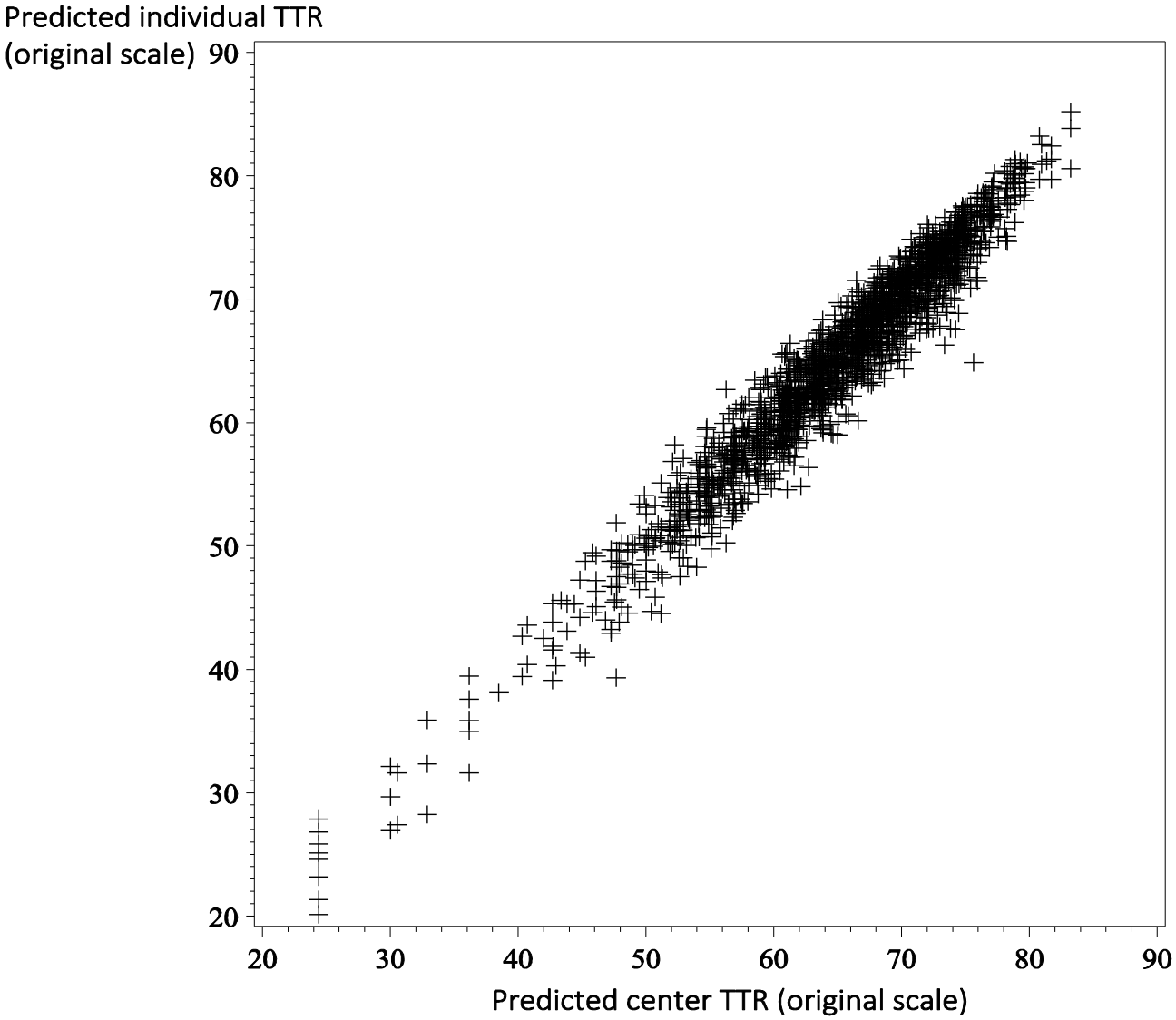
Supplemental Figure 1
The variability in center based TTR (cTTR) by country with cTTR predicted according to the mixed model with a fixed effect for country and random effect for center (Countries with less than 10 sites were excluded to simplify the plot).



Supplemental Figure 2

Correlation between predicted individual TTR (iTTR) and predicted center based TTR (cTTR)



Supplemental Table 1

Endpoints by predicted Center TTR (cTTR) for Vitamin K Antagonist (VKA) experienced patients

Predicted Center TTR	Apixaban N	Apixaban Events	Apixaban Rate/100 person yrs	Warfarin N	Warfarin Events	Warfarin Rate/100 person yrs	Apixaban vs. Warfarin HR	95% CI	Interaction (RCS) p-value
Primary Outcome									0.065
24.3-60.5	836	23	1.57	859	36	2.42	0.65	0.38, 1.09	
60.6-66.3	1147	24	1.13	1147	33	1.56	0.73	0.43, 1.23	
66.4-71.1	1554	21	0.76	1543	43	1.60	0.47	0.28, 0.80	
71.2-83.2	1671	34	1.08	1644	26	0.84	1.29	0.78, 2.15	
Total Death									0.19
24.3-60.5	836	57	3.77	859	61	3.96	0.95	0.66, 1.36	
60.6-66.3	1147	73	3.38	1147	72	3.34	1.01	0.73, 1.40	
66.4-71.1	1554	86	3.06	1543	115	4.17	0.73	0.55, 0.97	
71.2-83.2	1671	83	2.61	1644	88	2.81	0.93	0.69, 1.26	
Primary Safety Outcome									0.56
24.3-60.5	833	18	1.31	855	32	2.31	0.57	0.32, 1.01	
60.6-66.3	1146	32	1.61	1145	60	3.08	0.52	0.34, 0.80	
66.4-71.1	1548	64	2.53	1541	78	3.22	0.79	0.57, 1.10	
71.2-83.2	1669	71	2.47	1639	104	3.64	0.68	0.50, 0.92	
Net Clinical Benefit									0.49
24.3-60.5	836	81	5.60	859	102	6.99	0.80	0.60, 1.07	
60.6-66.3	1147	123	5.93	1147	144	7.03	0.85	0.66, 1.08	
66.4-71.1	1554	166	6.19	1543	207	7.97	0.78	0.63, 0.95	
71.2-83.2	1671	186	6.18	1644	205	6.88	0.90	0.74, 1.09	
SSE or Major Bleeding									0.30
24.3-60.5	836	36	2.68	859	59	4.37	0.61	0.41, 0.93	
60.6-66.3	1147	52	2.68	1147	82	4.32	0.62	0.44, 0.88	
66.4-71.1	1554	81	3.27	1543	106	4.49	0.73	0.55, 0.97	
71.2-83.2	1671	101	3.59	1644	119	4.24	0.84	0.65, 1.10	

Supplemental Table 2

Endpoints by predicted Individual TTR (iTTR) for Vitamin K Antagonist (VKA) experienced patients

Predicted iTTR	Apixaban N	Apixaban Events	Apixaban Rate/100 person yrs	Warfarin N	Warfarin Events	Warfarin Rate/100 person yrs	Apixaban vs. Warfarin HR	95% CI	Interaction (RCS) p-value
Primary Outcome									0.080
15.1-59.9	1582	53	1.91	1545	67	2.53	0.76	0.53, 1.08	
60.0-65.9	1169	40	1.84	1160	35	1.60	1.14	0.73, 1.80	
66.0-71.2	734	11	0.77	778	15	0.97	0.78	0.36, 1.71	
71.3-85.3	427	6	0.69	405	10	1.22	0.57	0.21, 1.58	
Total Death									0.89
15.1-59.9	1582	130	4.55	1545	144	5.20	0.87	0.69, 1.11	
60.0-65.9	1169	101	4.48	1160	108	4.82	0.93	0.71, 1.22	
66.0-71.2	734	51	3.48	778	58	3.71	0.94	0.64, 1.37	
71.3-85.3	427	22	2.49	405	23	2.76	0.90	0.50, 1.62	
Primary Safety Outcome									0.22
15.1-59.9	1574	42	1.68	1544	75	3.20	0.53	0.36, 0.77	
60.0-65.9	1164	49	2.48	1151	63	3.31	0.75	0.52, 1.09	
66.0-71.2	728	39	3.04	773	36	2.66	1.14	0.72, 1.79	
71.3-85.3	426	12	1.49	404	14	1.87	0.80	0.37, 1.73	
Net Clinical Benefit									0.86
15.1-59.9	1582	195	7.16	1545	237	9.22	0.78	0.65, 0.94	
60.0-65.9	1169	161	7.56	1160	168	7.97	0.95	0.76, 1.18	
66.0-71.2	734	94	6.87	778	108	7.38	0.93	0.70, 1.22	
71.3-85.3	427	37	4.38	405	42	5.28	0.83	0.53, 1.29	
SSE or Major Bleeding									0.53
15.1-59.9	1582	83	3.41	1545	117	5.16	0.67	0.50, 0.89	
60.0-65.9	1169	76	3.94	1160	87	4.65	0.85	0.62, 1.15	
66.0-71.2	734	45	3.57	778	48	3.62	0.98	0.65, 1.48	
71.3-85.3	427	17	2.15	405	23	3.14	0.69	0.37, 1.29	