Relationship Between Time in Therapeutic Range and Comparative Treatment Effect of Rivaroxaban and Warfarin: Results From the ROCKET AF Trial

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Relationship Between Time in Therapeutic Range and Comparative Treatment Effect of Rivaroxaban and Warfarin: Results From the ROCKET AF Trial

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Background—Time in therapeutic range (TTR) is a standard quality measure of the use of warfarin. We assessed the relative effects of rivaroxaban versus warfarin at the level of trial center TTR (cTTR) since such analysis preserves randomized comparisons.

Methods and Results—TTR was calculated using the Rosendaal method, without exclusion of international normalized ratio (INR) values performed during warfarin initiation. Measurements during warfarin interruptions >7 days were excluded. INRs were performed via standardized finger-stick point-of-care devices at least every 4 weeks. The primary efficacy endpoint (stroke or non-central nervous system embolism) was examined by quartiles of cTTR and by cTTR as a continuous function. Centers with the highest cTTRs by quartile had lower-risk patients as reflected by lower CHADS2 scores (P=0.0001) and a lower prevalence of prior stroke or transient ischemic attack (P=0.0001). Sites with higher cTTR were predominantly from North America and Western Europe. The treatment effect of rivaroxaban versus warfarin on the primary endpoint was consistent across a wide range of cTTRs (P value for interaction=0.71). The hazard of major and non-major clinically relevant bleeding increased with cTTR (P for interaction=0.001), however, the estimated reduction by rivaroxaban compared with warfarin in the hazard of intracranial hemorrhage was preserved across a wide range of threshold cTTR values.

Conclusions—The treatment effect of rivaroxaban compared with warfarin for the prevention of stroke and systemic embolism is consistent regardless of cTTR. (J Am Heart Assoc. 2014;3:e000521 doi: 10.1161/JAHA.113.000521)

Key Words: rivaroxaban • time in therapeutic range • warfarin

Vitamin K antagonists (VKAs) have formed the basis for the prevention of stroke and systemic embolus in patients with atrial fibrillation (AF) for several decades.1 The major impediment to VKA use is the unpredictability of the level of anticoagulation at a given dose. The international normalized ratio (INR) has been introduced as a measure of anticoagulation that enables the clinician and patient to monitor the degree of anticoagulation when VKAs are used. When the INR is <1.8 the risk of stroke and systemic embolism increases, and when the INR is >3.5 the risk of bleeding increases.2 This range includes the standard range of INR 2.0 to 3.0 widely recommended for VKA treatment for patients with AF.3,4

The estimated time in the therapeutic range (TTR) of INR 2.0 to 3.0 has become a widely applied measure of the quality of VKA anticoagulation in patients with AF, with most studies using Rosendaal’s interpolation method of calculating TTR.5 Several studies have shown a direct relationship between TTR...
and lower rates of stroke and systemic embolism in patients
with AF, while the relationship to bleeding risk has been more
variable.6,7 The ROCKET AF (Rivaroxaban Once Daily Oral
Direct Factor Xa Inhibition Compared with Vitamin K Antag-
onism for Prevention of Stroke and Embolism Trial in Atrial
Fibrillation) trial had a prospective analysis plan to estimate
the relationship between TTR and the treatment effect of
rivaroxaban compared with warfarin.

ROCKET AF was a blinded randomized trial that directly
compared warfarin treatment with a novel factor Xa inhibitor,
rivaroxaban.8 While TTR was measurable in the warfarin-
treated participants in the ROCKET AF trial, it is not an
appropriate measure of anticoagulation in patients treated
with factor Xa inhibitors. As a result, it becomes problematic
to compare rivaroxaban-treated patients with warfarin-treated
patients who are grouped by individual-level TTR values. The
ROCKET AF trial prespecified the alternative approach of
comparing the treatment effects of rivaroxaban versus
warfarin stratified by center-level TTR, thereby preserving
randomized comparisons.

Methods

Trial Design

The design and primary results of ROCKET AF have been
published.8,9 In brief, ROCKET AF was a multicenter, random-
ized, double-blind, double-dummy, event-driven trial comparing
rivaroxaban 20 mg daily (or 15 mg daily in patients with
creatinine clearance 30 to 49 mL/min) with dose-adjusted
warfarin (target INR 2.0 to 3.0) for prevention of all stroke
(ischemic or hemorrhagic) and systemic embolism.8 A double-
blind design was chosen to minimize bias in co-interventions
and reporting of clinical events. To maintain blinding, the
INRatio (HemoSense) point-of-care device was used to generate
real INR or sham values. The sham INR results were generated
using a validated algorithm that reflected the distribution of INR
values in a population of patients taking warfarin with clinical
characteristics similar to the study population.9 A double-
blind design was chosen to minimize bias in co-interventions
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using a validated algorithm that reflected the distribution of INR
values in a population of patients taking warfarin with clinical
characteristics similar to the study population.9 The doses of
warfarin and matching placebo tablets were titrated by the
investigators based on these values.9

The trial was supported by research grants from Johnson &
Johnson Pharmaceutical Research & Development and Bayer
HealthCare AG. The Duke Clinical Research Institute in
Durham, NC coordinated the trial and performed the statisti-
cal analyses for this manuscript independent of the spon-
sors. All appropriate national regulatory agencies and ethics/
institutional review boards at each participating center
approved the study. An international, multispecialty executive
committee, designed the study and takes responsibility for
the accuracy and completeness of all data and subsequent
analyses.

Measurement of INR

The INR was measured prior to randomization. Subjects were
randomized when the INR was <3.0. Post-randomization INR
monitoring was performed using the blinded point-of-care
device. The ROCKET AF protocol recommended that INR
monitoring be performed as clinically indicated, but no less
frequently than every 4 weeks.

Calculation of TTR

We present TTR using the method of Rosendaal and
colleagues, without exclusion of INR values obtained during
the period at the start of study-assigned warfarin therapy or
during temporary discontinuations.9 We present analyses
generated using models within those subgroups. The geo-
graphic regions were the same as those described in the main
trial results.8 Comparison of these risk relationships across
cTTR quartiles was achieved using a model that contained
treatment, cTTR quartile, and their interaction. For further
examination of the association of risk relationship to cTTR, a
series of models was generated at different cTTR thresholds,
and the interaction in all centers with cTTR at or above a certain value,
ranging from 0% to 80%. All models were adjusted for
geographic region, except subgroup models within regions.
Risk relationships are expressed as hazard ratios with 95%
confidence intervals. The probability of having an event by
1 year was also derived from the Cox models.

Statistical Methods

Baseline characteristics are shown as median (25th, 75th
percentiles) for continuous variables and as percent (num-
ber) for categorical variables, and were compared among
cTTR quartiles using Kruskal-Wallis tests for continuous
variables and Pearson chi-square tests for categorical
variables.

The risk of outcomes for patients randomized to rivarox-
aban versus warfarin was assessed using Cox proportional
hazards models with treatment as a covariate and using
robust sandwich variance estimators to account for correla-
tion within centers. All analyses were done in the safety on-
treatment population. The on-treatment period was defined as
the period during which the study drug was taken plus 2
days following permanent study drug discontinuation (ie, from
initial study drug dose to last dose plus 2 days). Safety analyses
included patients from a good clinical practice (GCP)-violating
site while efficacy analyses excluded these patients (n=93).
Risk relationships within regions or within cTTR quartiles were
generated using models within those subgroups. The geo-
graphic regions were the same as those described in the main
trial results.8 Comparison of these risk relationships across
cTTR quartiles was achieved using a model that contained
treatment, cTTR quartile, and their interaction. For further
examination of the association of risk relationship to cTTR, a
series of models was generated at different cTTR thresholds,
ie, among all centers with cTTR at or above a certain value,
ranging from 0% to 80%. All models were adjusted for
geographic region, except subgroup models within regions.
Risk relationships are expressed as hazard ratios with 95%
confidence intervals. The probability of having an event by
1 year was also derived from the Cox models.

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Journal of the American Heart Association 2
Results

Baseline Characteristics

ROCKET AF enrolled a high-risk population with many risk factors for stroke and systemic embolism. Among the 14,264 randomized patients, the median age was 73 years, mean CHADS<sub>2</sub> score was 3.5, 55% had prior thromboembolism, and 62.5% had heart failure. Among the 7,133 randomized to warfarin, 7,025 had INR data and the mean individual TTR in warfarin patients was 55%. The distribution of cTTR across all sites is shown in Figure 1. The mean cTTR was 59% and the median was 61% (25th, 75th: 51%, 69%). The baseline characteristics of the patients according to quartiles of cTTR are shown in Table 1. Centers with higher cTTR had lower-risk patients as evidenced by lower CHADS<sub>2</sub> scores ($P<0.0001$) and a lower prevalence of prior stroke or transient ischemic attack (TIA) ($P<0.0001$). Centers with higher cTTR were from regions with middle- and high-income countries, including Western Europe and North America.

Geographic Variation in cTTR

The mean cTTR varied across geographic regions, as shown in Table 2. The highest mean cTTR occurred in North America (65%) and the lowest was observed in the Asia-Pacific region and Eastern Europe (52%).

Outcomes and cTTR

The primary efficacy outcome (stroke or non-central nervous system [CNS] embolism) for rivaroxaban versus warfarin is shown across the quartiles of cTTR in Table 3. Rates of stroke or non-CNS embolism decreased with higher cTTR. The treatment effect with rivaroxaban on the primary endpoint across cTTR quartiles was consistent ($P$ for interaction = 0.71). The hazard ratio (HR) for the primary efficacy endpoint was 0.70 (95% confidence interval [CI] 0.47 to 1.04) in the lowest quartile of cTTR and 0.73 (0.50 to 1.06) in the highest quartile of cTTR. We repeated these analyses for the endpoint of ischemic stroke or non-CNS systemic embolism and the results again showed no evidence of heterogeneity across cTTR quartiles (Table 4, interaction $P$ = 0.86).

The lowest HR for the primary endpoint (rivaroxaban versus warfarin) was observed in the region with the highest cTTR (North America HR 0.61 [95% CI 0.35 to 1.06]). There was no evidence of an interaction between region and treatment ($P$ for interaction = 0.62).

As shown in Table 5, the rates of the primary safety endpoint (major and non-major clinically relevant bleeding) increased with higher cTTR. In the lowest quartile of cTTR, rivaroxaban was associated with a lower hazard of bleeding (HR 0.80 [95% CI 0.66 to 0.98]), while in the top quartile of cTTR, rivaroxaban was associated with a higher hazard.
## Table 1. Baseline Characteristics According to Quartiles of cTTR

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>cTTR Q1 (0.0% to 50.6%) (N=3430)</th>
<th>cTTR Q2 (50.7% to 58.5%) (N=3563)</th>
<th>cTTR Q3 (58.6% to 65.7%) (N=3496)</th>
<th>cTTR Q4 (65.7% to 100%) (N=3508)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70 (62, 76)</td>
<td>72 (64, 77)</td>
<td>74 (66, 78)</td>
<td>75 (68, 80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>44% (1506)</td>
<td>41% (1450)</td>
<td>39% (1368)</td>
<td>35% (1222)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White</td>
<td>73% (2490)</td>
<td>85% (3011)</td>
<td>83% (2904)</td>
<td>92% (3231)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1% (33)</td>
<td>2% (56)</td>
<td>2% (55)</td>
<td>1% (34)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>22% (767)</td>
<td>11% (393)</td>
<td>13% (441)</td>
<td>5% (169)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4% (140)</td>
<td>3% (103)</td>
<td>3% (96)</td>
<td>2% (74)</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asia/Pacific Islands</td>
<td>22% (766)</td>
<td>11% (405)</td>
<td>13% (462)</td>
<td>13% (455)</td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>57% (1947)</td>
<td>50% (1797)</td>
<td>35% (1210)</td>
<td>12% (426)</td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>11% (378)</td>
<td>16% (556)</td>
<td>16% (573)</td>
<td>10% (359)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>5% (182)</td>
<td>12% (417)</td>
<td>17% (592)</td>
<td>40% (1417)</td>
<td></td>
</tr>
<tr>
<td>Western Europe</td>
<td>5% (157)</td>
<td>11% (388)</td>
<td>19% (659)</td>
<td>24% (851)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.7 (24.7, 31.6)</td>
<td>28.2 (25.1, 31.8)</td>
<td>28.3 (25.1, 32.0)</td>
<td>28.7 (25.6, 32.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP, mean (SD)</td>
<td>132.7 (15.6)</td>
<td>132.2 (15.9)</td>
<td>132.1 (16.4)</td>
<td>131.6 (17.1)</td>
<td>0.0031</td>
</tr>
<tr>
<td>AF type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Persistent</td>
<td>81% (2788)</td>
<td>82% (2930)</td>
<td>79% (2761)</td>
<td>82% (2688)</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>18% (604)</td>
<td>17% (600)</td>
<td>20% (685)</td>
<td>16% (575)</td>
<td></td>
</tr>
<tr>
<td>New onset</td>
<td>1% (38)</td>
<td>1% (33)</td>
<td>1% (50)</td>
<td>2% (65)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>90% (3100)</td>
<td>92% (3276)</td>
<td>91% (3180)</td>
<td>89% (3115)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>37% (1262)</td>
<td>39% (1365)</td>
<td>42% (1454)</td>
<td>42% (1460)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>58% (1995)</td>
<td>53% (1891)</td>
<td>51% (1798)</td>
<td>47% (1657)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHF</td>
<td>71% (2448)</td>
<td>70% (2478)</td>
<td>61% (2129)</td>
<td>49% (1711)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR (MDRD)</td>
<td>69.4 (57.1, 81.0)</td>
<td>68.6 (56.7, 81.6)</td>
<td>66.6 (55.9, 78.5)</td>
<td>68.4 (56.3, 78.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.3 (13.2, 15.4)</td>
<td>14.2 (13.2, 15.2)</td>
<td>14.2 (13.1, 15.2)</td>
<td>14.1 (13.1, 15.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD</td>
<td>20% (686)</td>
<td>21% (754)</td>
<td>23% (816)</td>
<td>29% (1018)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD</td>
<td>10% (347)</td>
<td>10% (345)</td>
<td>10% (348)</td>
<td>12% (417)</td>
<td>0.010</td>
</tr>
<tr>
<td>PAD</td>
<td>6% (193)</td>
<td>5% (169)</td>
<td>6% (227)</td>
<td>6% (227)</td>
<td>0.0039</td>
</tr>
<tr>
<td>Prior GI bleed</td>
<td>2% (80)</td>
<td>2% (60)</td>
<td>4% (151)</td>
<td>6% (195)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Liver disease</td>
<td>7% (252)</td>
<td>4% (158)</td>
<td>5% (187)</td>
<td>4% (137)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol consumption (past 12 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinent</td>
<td>75% (2586)</td>
<td>69% (2454)</td>
<td>64% (2227)</td>
<td>51% (1793)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Light</td>
<td>22% (747)</td>
<td>27% (956)</td>
<td>31% (1096)</td>
<td>41% (1430)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>2% (71)</td>
<td>3% (122)</td>
<td>4% (147)</td>
<td>7% (263)</td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>1% (26)</td>
<td>1% (31)</td>
<td>1% (25)</td>
<td>1% (21)</td>
<td></td>
</tr>
<tr>
<td>CHADS₂, mean (SD)</td>
<td>3.5 (0.9)</td>
<td>3.5 (0.9)</td>
<td>3.5 (1.0)</td>
<td>3.3 (1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHADS₂ score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>11% (364)</td>
<td>11% (383)</td>
<td>13% (446)</td>
<td>18% (641)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>42% (1456)</td>
<td>45% (1597)</td>
<td>43% (1511)</td>
<td>44% (1541)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>32% (1102)</td>
<td>29% (1035)</td>
<td>29% (1006)</td>
<td>25% (872)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>13% (456)</td>
<td>14% (484)</td>
<td>13% (444)</td>
<td>11% (384)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2% (52)</td>
<td>2% (64)</td>
<td>3% (89)</td>
<td>2% (70)</td>
<td></td>
</tr>
<tr>
<td>VKA use at screening</td>
<td>41% (1403)</td>
<td>56% (1998)</td>
<td>69% (2400)</td>
<td>83% (2925)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic aspirin at screening</td>
<td>45% (1542)</td>
<td>41% (1446)</td>
<td>32% (1127)</td>
<td>29% (1005)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Continuous variables are shown as median (25th, 75th percentiles), except where noted. Categorical variables are shown as percent (number). P value is from Pearson chi-square test for categorical variables, from Kruskal-Wallis test for continuous variables. AF indicates atrial fibrillation; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; cTTR, center-level time in therapeutic range; eGFR, glomerular filtration rate; GI, gastrointestinal; MDRD, Modification of Diet in Renal Disease; PAD, peripheral arterial disease; SD, standard deviation; TIA, transient ischemic attack; VKA, Vitamin K antagonist.
Table 2. Mean cTTR and Treatment Effect Across Geographic Regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean TTR (%)</th>
<th>Primary Efficacy Endpoint (Safety On-Treatment Population) HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>65</td>
<td>0.61 (0.35, 1.06)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>64</td>
<td>0.87 (0.52, 1.46)</td>
</tr>
<tr>
<td>Latin America</td>
<td>57</td>
<td>0.93 (0.62, 1.37)</td>
</tr>
<tr>
<td>Asia/Pacific Islands</td>
<td>52</td>
<td>0.67 (0.44, 1.03)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>52</td>
<td>0.88 (0.67, 1.19)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; cTTR, center-level time in therapeutic range; HR, hazard ratio.

The population for this analysis was the safety on-treatment population from sites with calculable cTTR. cTTR was calculated from all ITT warfarin patients at each center. All analyses are based on the time to first event. Event rates are the number of events per 100 patient-years of follow-up. HRs (95% CIs) are derived from a proportional hazards model with treatment as a covariate. CNS indicates central nervous system; cTTR, center-level time in therapeutic range; J, number of subjects in each subgroup; n, number of subjects with events.

Discussion

TTR is a widely used measure of quality of anticoagulation with warfarin. In the ROCKET AF trial the TTR correlated negatively with risk of stroke and systemic embolism, although TTR correlated positively with risk of bleeding. However, despite a wide variation of TTR levels across centers in the trial there was no evidence that the relative efficacy of rivaroxaban versus warfarin varied by cTTR.

TTR is impacted by a host of factors. Multiple comorbidities such as heart failure, liver and lung disease, and renal disease can alter INR control. While none of these individually have a major impact on TTR, in aggregate they have a significant impact. Perhaps more important is the adherence of the patient, which is dependent on many social, cultural, financial, and individual behavioral characteristics in addition to the direction of the prescriber. Some studies have shown that instrumental factors such as distance between the clinic and home and availability of transportation are important. We recently published the finding that the region, and more importantly, the country involved has a major impact on TTR, far outweighing all the other factors routinely measured in clinical practice or clinical trials. A recent analysis from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial found that much of the variation in cTTR values could be explained by whether or not an algorithmic approach to warfarin management was used.

The relationships among TTR, outcomes, and treatment effect in the ROCKET AF trial cannot be directly assessed at the individual patient level using iTTR since it is not meaningful in patients treated with rivaroxaban. Furthermore, because TTR is a post-randomization covariate, patients with different TTR levels are likely to have different levels of stroke and bleeding risk independent of TTR. Identifying appropriate comparator patients assigned to rivaroxaban (for whom INR values are not available) is not possible with suitable accuracy, so using it to adjust the estimate of treatment effect violates usual principles of analysis and abrogates the advantages gained by randomization. Because of these concerns, we and others have compared patients assigned to

Table 3. Stroke and Non-CNS Embolism by Quartiles of cTTR

<table>
<thead>
<tr>
<th>Center TTR</th>
<th>Rivaroxaban (N=6891)</th>
<th>Warfarin (N=7080)</th>
<th>Rivaroxaban vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event Rate (100 Pt-Years) n/J (%)</td>
<td>Event Rate (100 Pt-Years) n/J (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>0.00% to 50.6%</td>
<td>45/1735 (2.6) 1.8</td>
<td>62/1689 (3.7) 2.5</td>
<td>0.70 (0.47, 1.04)</td>
</tr>
<tr>
<td>50.7% to 58.5%</td>
<td>53/1746 (3.0) 1.9</td>
<td>63/1807 (3.5) 2.2</td>
<td>0.90 (0.64, 1.26)</td>
</tr>
<tr>
<td>58.6% to 65.7%</td>
<td>54/1734 (3.1) 1.9</td>
<td>62/1758 (3.5) 2.1</td>
<td>0.88 (0.62, 1.25)</td>
</tr>
<tr>
<td>65.7% to 100.0%</td>
<td>37/1676 (2.2) 1.3</td>
<td>55/1826 (3.0) 1.8</td>
<td>0.73 (0.50, 1.06)</td>
</tr>
</tbody>
</table>

The population for this analysis was the safety on-treatment population from sites with calculable cTTR. cTTR was calculated from all ITT warfarin patients at each center. All analyses are based on the time to first event. Event rates are the number of events per 100 patient-years of follow-up. HRs (95% CIs) are derived from a proportional hazards model with treatment as a covariate. CNS indicates central nervous system; cTTR, center-level time in therapeutic range; J, number of subjects in each subgroup; n, number of subjects with events.

*The P value for the interaction of treatment group and center-based INR control group based on the Cox proportional hazard model including treatment group, center-based INR control group, and their interaction.
rivaroxaban and warfarin stratified by center-level TTR, where the analysis still benefits from randomization. However, analysis at the center level allows only indirect inference about the effect of individual-level TTR, ie, iTTR. Moreover, our analysis demonstrated that centers with higher cTTR have patients with different comorbidity profiles, including lower-risk patients as indicated by lower CHADS2 scores and lower event rates even among the centers’ patients taking rivaroxaban.

While we saw no overall relationship between cTTR and the relative effect of rivaroxaban versus warfarin, we did not have sufficient power to specifically examine centers achieving TTR levels above 70. Analyses from the large RE-LY and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trials also found no relationship between cTTR and the estimate of the treatment effect, including sites with cTTR >70.16,17

The increase in bleeding that we observed in centers with higher cTTR levels is consistent with higher INR levels seen in such centers. Worldwide in centers with poor TTR, the most common deviation is almost always with persistent low values rather than high values. This likely explains the preservation of the benefit for intracranial hemorrhage regardless of cTTR. Some regions of the world have more aversion to bleeding than others leading to more cautious adjustments to VKA doses.18,19

One consideration in understanding the cTTR values is the actual observed event rates in the trial on warfarin therapy. In ROCKET AF, the observed event rates for a CHADS2 score of 2 was 1.7, for CHADS2 score of ≥3 was 2.6, and for prior stroke patients was 2.9 events per 100 patient-years versus 1.4, 2.8, and 3.2 in the ARISTOTLE trial which had a higher TTR on average. These data provide additional support for the concept that cTTR depends on a complex mix of factors, with practitioner skill being only one of them. For example, simply measuring more INRs will lead to a higher TTR, assuming that appropriate changes in doses are made. In countries with closer proximity of clinics to patients and with fewer cost constraints, INRs tend to be measured more frequently.

The question of whether there is a cTTR that is too low to allow for a valid direct comparison of a new anticoag-

<table>
<thead>
<tr>
<th>Center TTR</th>
<th>Rivaroxaban (N=6891)</th>
<th>Warfarin (N=7080)</th>
<th>Rivaroxaban vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/J (%)</td>
<td>Event Rate (100 Pt-Year)</td>
<td>n/J (%)</td>
</tr>
<tr>
<td>0.00% to 50.6%</td>
<td>38/1735 (2.2)</td>
<td>1.5</td>
<td>49/1689 (2.9)</td>
</tr>
<tr>
<td>50.7% to 58.5%</td>
<td>40/1746 (2.3)</td>
<td>1.5</td>
<td>46/1807 (2.6)</td>
</tr>
<tr>
<td>58.6% to 65.7%</td>
<td>43/1734 (2.5)</td>
<td>1.5</td>
<td>46/1758 (2.6)</td>
</tr>
<tr>
<td>65.7% to 100.0%</td>
<td>33/1676 (2.0)</td>
<td>1.2</td>
<td>41/1826 (2.3)</td>
</tr>
</tbody>
</table>

The population for this analysis was the safety on-treatment population from sites with calculable cTTR. cTTR was calculated from all ITT warfarin patients at each center. All analyses are based on the time to first event. Event rates are the number of events per 100 patient-years of follow-up. HRs (95% CIs) are derived from a proportional hazards model with treatment as a covariate. CNS indicates central nervous system; cTTR, center-level time in therapeutic range; J, number of subjects in each subgroup; n, number of subjects with events.

*The P value for the interaction of treatment group and center-based INR control group based on the Cox proportional hazard model including treatment group, center-based INR control group, and their interaction.

<table>
<thead>
<tr>
<th>Center TTR</th>
<th>Rivaroxaban (N=6941)</th>
<th>Warfarin (N=7032)</th>
<th>Rivaroxaban vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/J (%)</td>
<td>Event Rate (100 Pt-Years)</td>
<td>n/J (%)</td>
</tr>
<tr>
<td>0.00% to 50.71%</td>
<td>271/1780 (15.2)</td>
<td>11.30</td>
<td>315/1734 (18.2)</td>
</tr>
<tr>
<td>50.89% to 58.44%</td>
<td>285/1731 (16.5)</td>
<td>11.72</td>
<td>313/1785 (17.5)</td>
</tr>
<tr>
<td>58.46% to 65.66%</td>
<td>381/1741 (21.9)</td>
<td>15.10</td>
<td>378/1765 (21.4)</td>
</tr>
<tr>
<td>65.71% to 100.0%</td>
<td>484/1689 (28.7)</td>
<td>20.61</td>
<td>443/1839 (24.1)</td>
</tr>
</tbody>
</table>

The population for this analysis was safety on-treatment patients from sites with calculable cTTR. cTTR was calculated from all ITT warfarin patients at each center. All analyses are based on the time to first event. Event rates are the number of events per 100 patient-years of follow-up. HRs (95% CIs) are derived from a proportional hazards model with treatment as a covariate. CNS indicates central nervous system; cTTR, center-level time in therapeutic range; J, number of subjects in each subgroup; n, number of subjects with events.

*The P value for the interaction of treatment group and center-based INR control group based on the Cox proportional hazard model including treatment group, center-based INR control group, and their interaction.
ulant with warfarin merits serious consideration. At the extreme, if cTTR was very low, one would expect the comparator treatment to be superior if it was effective. While no direct measure of TTR was available in most of the controlled trials of warfarin in AF, best estimates using meta-analysis indicate a TTR in the range of 61%.20 The average TTR in US practice is 55% and recent data indicate that in clinical practice, TTR values are typically below 60%.2,21 Furthermore, the region with the highest TTR (North America), had the largest point estimate for treatment difference in favor of rivaroxaban, a finding that was not statistically significant, but the existing trend favors no impact of cTTR on estimates of the rivaroxaban treatment effect.

Limitations
The limitations of this analysis should be considered. These results emanate from a randomized, blinded trial at selected centers in a high-risk population. TTR is a post-randomization variable and therefore, the entire analysis has uncertainties and should be considered to provide a perspective akin to a sensitivity analysis. Furthermore, the analysis of cTTR in this study and in other trials has limited power.

Conclusion
TTR is an important and validated quality measure for VKA management. However, TTR does not impact the estimate of the treatment effect of rivaroxaban versus warfarin for the prevention of stroke and systemic embolism. The consistency of this finding with other major trials of novel anticoagulants versus warfarin16,17 and the observation of expected event rates on warfarin treatment in ROCKET AF provide support for this conclusion. Regardless of the choice of anticoagulation, adherence factors related to education, cultural factors, economics, and transportation need to be considered in designing systems of care for stroke prevention as well as medical comorbidities and access to expert medical care from skilled clinicians.
Figure 3. Treatment effect for the reduction of stroke or non-CNS embolism in rivaroxaban and warfarin treated patients at a given cTTR threshold. The x-axis shows the threshold value for cTTR and the y-axis shows the HR for the time to stroke or non-CNS embolism for rivaroxaban vs warfarin given a certain threshold cTTR. The y-axis also shows the mean individual TTR in those centers that meet the threshold cTTR. There is instability in the estimate of the treatment effect at high cTTR thresholds due to smaller sample size, but no evidence that warfarin is superior to rivaroxaban in the prevention of stroke and systemic embolus at any cTTR threshold. CNS indicates central nervous system; cTTR, center time in therapeutic range; INR, international normalized ratio.

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centers that meet the threshold cTTR. There is instability in the estimate of the treatment effect at high cTTR thresholds due to smaller sample size, but no evidence that warfarin is superior to rivaroxaban in the prevention of stroke and systemic embolus at any cTTR threshold. CNS indicates central nervous system; cTTR, center time in therapeutic range; INR, international normalized ratio.

Figure 4. Risk of intracranial hemorrhage in rivaroxaban- vs warfarin-treated patients according to cTTR at a given threshold. The x-axis shows the threshold value for cTTR and the y-axis shows the HR for the time to stroke or non-CNS embolism for rivaroxaban vs warfarin given a certain threshold cTTR. The y-axis also shows the mean individual TTR in those centers that meet the threshold cTTR. There is instability in the estimate of the treatment effect at high cTTR thresholds due to smaller sample size, but no evidence that warfarin is superior to rivaroxaban in the prevention of stroke and systemic embolus at any cTTR threshold. CNS indicates central nervous system; cTTR, center time in therapeutic range; INR, international normalized ratio.

from Novartis, Merck, and Amilyn/Lilly; equity interest in Nitrox.

References


