Anticoagulation Control in Warfarin-Treated Patients Undergoing Cardioversion of Atrial Fibrillation (from the Edoxaban Versus Enoxaparin – Warfarin in Patients Undergoing Cardioversion of Atrial Fibrillation Trial)

Lip, Gregory; Al-Saady, Naab; Jin, James; Sun, Ming; Melino, Michael; Winters, Shannon M.; Zamoryakhin, Dmitry; Goette, Andreas

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Anticoagulation Control in Warfarin Treated Patients Undergoing Cardioversion for Atrial Fibrillation

(From the ENSURE-AF trial)

Running Title: Anticoagulation Control in Cardioversion of AF

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Abstract

In the ENSURE-AF study (NCT 02072434), edoxaban was compared to enoxaparin–warfarin in 2199 patients undergoing electrical cardioversion of non-valvular atrial fibrillation (AF). In this multicenter PROBE trial, we analyzed patients randomized to enoxaparin–warfarin. We determined time to achieve therapeutic range (TtTR), time in therapeutic range (TiTR), their clinical determinants, relation to SAMe-TT$_2$R$_2$ score, and impact on primary endpoints (composite of stroke, systemic embolic event [SEE], myocardial infarction [MI], and cardiovascular death [CVD] and composite of major + clinically relevant non-major [CRNM] bleeding). Among 1104 patients randomized to enoxaparin—warfarin, 27% were oral anticoagulant naïve. Mean age was 64.2±11 years and mean CHA$_2$DS$_2$-VASc score was 2.6. Mean TtTR was 7.7 days (median 7 days) and mean TiTR after reaching INR 2.0–3.0 was 71%. In 695 patients with INR <2.0 prior to first dose and who reached ≥2.0, 436 had a SAMe-TT$_2$R$_2$ score ≤2 and 259 a score of >2. On multivariate regression, an independent predictor of extended TtTR was creatinine clearance (CrCl) \( P=0.02 \). TtTR was marginally related to stroke/SEE/MI/CVD \( P=0.06; \) OR=0.23, 95% CI 0.02–1.17 but not to any bleeding. Independent predictors of TiTR were prior VKA experience \( P<0.01 \) and low HAS-BLED score \( P=0.02 \). TiTR was related to any bleeding \( P=0.02; \) OR=0.39, 95% CI 0.16–0.88, but not stroke/SE/MI/CVD. In this cohort of warfarin users with a high TiTR no difference was seen between TtTR and TiTR in relation to SAMe-TT$_2$R$_2$ score. In conclusion, even in this short-term study, TiTR was significantly related to bleeding events.

**Key Words:** warfarin, time in therapeutic range, bleeding, stroke
Introduction

Effective stroke prevention in patients with atrial fibrillation (AF) requires the use of oral anticoagulation. In the historical randomized trials, the use of warfarin significantly reduced the risk of stroke (by 64%) and all-cause mortality (by 26%) when compared with placebo or control. However, the effectiveness and safety of warfarin is dependent upon the quality of anticoagulation control (time in therapeutic range [TiTR]) even in the presence of a single stroke risk factor. Optimization of TiTR is dependent on many factors and the most common are included in the SAMe-TT$_2$R$_2$ score. This score has been validated to aid clinical decision-making and has been shown to be predictive of labile INRs, bleeding, thromboembolism, and death, consequences of poor anticoagulation control. In the ENSURE-AF study, the oral factor Xa inhibitor edoxaban was compared to warfarin in 2199 patients undergoing electrical cardioversion of non-valvular AF. Ideal patient management requires optimization of warfarin therapy within a therapeutic range of international normalized ratio (INR) 2.0–3.0, especially in the peri-cardioversion period. Given the prospectively collected data in ENSURE-AF, we determined aspects of anticoagulation control in the warfarin arm of this randomized trial, in an ancillary analysis.

Methods

The design and principal results of the ENSURE-AF trial (NCT 02072434) have been published. In brief, this was a multicenter, prospective, randomized, open-label, blinded-endpoint evaluation, parallel group Phase 3b clinical trial, in which patients with non-valvular AF undergoing electrical cardioversion were randomized to edoxaban or warfarin. Patients with an INR <2.0 at randomization received enoxaparin and daily warfarin until the INR was ≥2.0 and those with INR ≥2.0 at the time of randomization did not require enoxaparin and were treated with warfarin alone. Patients were stratified by anticoagulation strategy (transoesophageal echocardiography [TEE] or non-TEE strata, or whether
previously anticoagulation naïve or experienced, selected edoxaban dose, and region, as defined at randomization). For the present study, we confined our investigation to an analysis of the 1104 patients in the ENSURE-AF trial who were randomized to enoxaparin–warfarin.

We determined the TtTR, TtTR, their clinical determinants and impact on efficacy and safety outcomes. For patients who had baseline INR <2.0 and reached INR ≥2.0 during the on-treatment period, TtTR was defined as the first date of INR ≥2.0 minus the date of first study drug administration. For patients who had 2.0 ≥ INR ≤ 3.0 during the on-treatment period, TtTR was defined as the percent of time in therapeutic range (2.0 ≥ INR ≤ 3.0) from the first date of 2.0 ≥ INR ≤ 3.0.

Stroke and bleeding risk was defined by the CHA\textsubscript{2}DS\textsubscript{2}-VASc\textsuperscript{11} and HAS-BLED\textsuperscript{12} scores, respectively, while the SAMe-TT\textsubscript{2}R\textsubscript{2} score\textsuperscript{5} was defined as summarized in the Data Supplement.

The primary efficacy analysis was comparing the occurrence of a composite endpoint of stroke, systemic embolic event (SEE), myocardial infarction (MI), and cardiovascular death (CVD) between the edoxaban group and the enoxaparin–warfarin group from randomization to end of follow-up and was performed on the intention-to-treat population (all individuals who were enrolled into the study and randomly assigned). The primary safety endpoint of the trial was the composite of major + clinically relevant non-major (CRNM) bleeding which occurred during the on treatment period, defined as the time period the patient was taking study medication plus up to 3 days after the last dose for that time period. Any bleeding was defined as the composite of major + CRNM + minor bleeding from time of first administration of study drug to end of treatment +3 days. Patients were followed for 28 days on study drug after cardioversion + another 30 days to assess safety on an investigator-prescribed standard of care.

The protocol and its amendments were approved by ethics committees or institutional review boards. All patients provided written informed consent prior to participation in the study.
Time to therapeutic range was calculated for a subset of patients who were randomized to enoxaparin–warfarin, had INR <2.0 prior to first dose, and reached therapeutic range of ≥2.0 during the on treatment period. Time in therapeutic range (TiTR) was calculated for patients receiving enoxaparin–warfarin who had INR between 2.0 and 3.0 during the on treatment period only. Mean TtTR and TiTR outcomes were provided for patients with SAMe-TT;R2 score ≤2 and >2, respectively. We also calculated time in therapeutic range by imputing between-visit INR using a linear interpolation method described by Rosendaal and colleagues.13

For enoxaparin–warfarin patients, the clinical characteristics were summarized and the difference between OAC naïve and experienced were assessed using 2 sample t-test or Chi-square test. The clinical determinants of TtTR and TiTR were analyzed by a linear model including covariates of age, gender, region, race, creatinine clearance (CrCl), cardioversion approach, ethnicity, oral anticoagulant (OAC) experience, CHA2DS2-VASc score, HAS-BLED score, smoking/tobacco use, and alcohol use. The TtTR and TiTR data were dichotomized to show the relation of TtTR and TiTR to efficacy and safety outcomes. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented.

Efficacy and safety outcomes were compared between the patients who received enoxaparin–warfarin and patients who received edoxaban from sites with mean TiTR ≤70% and >70%, respectively.

Results

Among 1104 patients randomized to enoxaparin–warfarin, 27% were naïve to OAC at randomization (Table 1). Mean age was 64.2 (standard deviation [SD] ±10.7) years and mean CHA2DS2-VASc score was 2.6 (SD ±1.4). Overall mean time in therapeutic range as calculated using the Rosendaal method was 60% (SD ±30.6) being higher in OAC-experienced patients versus OAC-naïve patients (P=0.001).
Mean TtTR was 7.7 days (median 7 days), with no difference between the OAC-experienced and OAC-naïve groups. Mean TiTR after reaching INR 2.0–3.0 on warfarin was 71%, which was significantly higher among patients who were OAC experienced ($P=0.0204$).

The SAMe-TT$_2$R$_2$ score was not significantly different between the OAC experienced and naïve patients ($P=0.777$) but the proportion of patients with SAMe-TT$_2$R$_2$ score >2 was higher in the OAC-experienced group ($P=0.0176$). In 695 patients with INR <2.0 prior to first dose and who reached therapeutic range of ≥2.0, 436 (63%) had a SAMe-TT$_2$R$_2$ score ≤2 and 259 (37%) had a SAMEe-TT$_2$R$_2$ score of >2. Mean TtTR in these SAMe-TT$_2$R$_2$ score subgroups were similar. In the 974 patients with INR in range of 2.0–3.0 post first dose, TiTR was 71% vs 70% for patients with SAMe-TT$_2$R$_2$ score ≤2 and >2, respectively.

On multivariate regression, an independent predictor of extended TtTR was CrCl ($P=0.017$). Independent predictors of TiTR were prior vitamin K antagonist (VKA) experience ($P=0.005$) and low HAS-BLED score ($P=0.019$) [Table 2].

On contingency table analysis, TtTR was marginally related to stroke/SEE/MI/CVD ($P=0.06$; OR [odds ratio]=0.23, 95% CI 0.02–1.17) but not to any bleeding ($P=0.53$; OR=0.72, 95% CI 0.28–1.80). TiTR was related to any bleeding ($P=0.02$; OR=0.39, 95% CI 0.16–0.88), but not stroke/SE/MI/CVD ($P=0.31$; OR=0.42, 95% CI 0.07–1.98) [Table 3]. Figure 1 illustrates these efficacy and safety outcomes in relation to TiTR.

**Discussion**

In this pre-specified analysis of a well-managed cohort of warfarin users in a clinical trial setting we found that the only independent determinant of TtTR was CrCl, while independent predictors of TiTR were prior VKA experience and low HAS-BLED score. Additionally, in this cohort with a high TiTR (>70%),...
no difference was observed between mean TtTR and TiTR in regards to the SAMe-TT$_2$R$_2$ score. Nevertheless, even in this short-term study, TiTR was related to bleeding events.

We found that an independent predictor of TtTR was CrCl, consistent with prior data showing the difficulties of managing warfarin in non-valvular AF patients with renal impairment. Improved TiTR in patients with prior VKA experience would be consistent with patients ‘experienced’ in handling and managing VKA, achieving better anticoagulation control—perhaps reflecting the impact of improved patient education and knowledge of potential food effects and drug interactions in this unblinded ‘open’ clinical trial design, while low HAS-BLED scores may reflect less comorbidities and polypharmacy, leading to improved TiTR.

These observations are relevant to the use of warfarin in a conventional (non-TEE) anticoagulation strategy for cardioversion, where there may be marked variability within and between patients in TtTR. This is of relevance given that delays in achieving therapeutic anticoagulation with a conventional warfarin strategy may prolong the time in AF, and could potentially extend the time to cardioversion and reduce the chance of successful cardioversion and maintenance of sinus rhythm.

The TiTR when warfarin is used can be influenced by many clinical factors. The most common of which have been incorporated into the SAMe-TT$_2$R$_2$ score. Various studies have shown how the SAMe-TT$_2$R$_2$ score can dichotomize those likely to do well on warfarin with a good TiTR (SAMe-TT$_2$R$_2$ score 0-2) versus those less likely to achieve good TiTR (SAMe-TT$_2$R$_2$ score >2). Furthermore, the validated SAMe-TT$_2$R$_2$ score is predictive of labile INRs, as well as the adverse outcomes associated with poor anticoagulation control, such as thromboembolism, death and bleeding. Nonetheless, in this cohort with a high TiTR (>70%), the SAMe-TT$_2$R$_2$ score did not discriminate between mean TtTR and TiTR. Similar findings were noted in another observational cohort with high TiTR, although the short follow-up and meticulous attention to achieving good TiTR may have reduced the predictive value of SAMe-
TT₂R₂ in this clinical trial. Given that the SAMe-TT₂R₂ score was designed to help discriminate those likely or not to achieve good (or poor) TiTR, the score seems to perform best in settings with a broad range of TiTR control.¹⁹ Recent data published by Pokorney et al²⁰ further suggest that prediction of stability for INR values among patients who receive long-term warfarin therapy is limited.

Time to therapeutic range was not significantly related to stroke/SEE/MI/CVD or any bleeding, and this may reflect the ENSURE-AF trial design, where enoxaparin bridging was used in patients wherever INRs were suboptimal to allow optimized warfarin management to be compared with edoxaban.⁹ Also, the short follow-up in this relatively low risk population of patients with non-valvular AF selected for cardioversion may have influenced event rates. However, even in this cohort with high TiTR, there was a significant relation of TiTR to any bleeding, but not stroke/SEE/MI/CVD. The non-significant impact on the latter may reflect the low overall event rates in the trial, and the short follow-up period. Nonetheless, TiTR is also a strong determinant of bleeding risks on VKA, and our data support this relationship.³

Although the ENSURE-AF trial is the largest study in AF peri-cardioversion to date, this study is limited by being a subgroup analysis of a selected clinical trial cohort, and the results may not be applicable to the general AF population. In the ‘real world’, adherence and quality of life on enoxaparin injections would be relevant considerations, but we mandated good adherence in this trial setting. Also, the low overall event rates and short follow-up period may have influenced outcome rates which may be underpowered. In the trial setting, much focus was made towards achieving good TTR (which was achieved, with TiTR >70%) and would not be reflective of ‘real world’ warfarin management in some healthcare settings.

The high rate of patients not achieving therapeutic range reflects the short nature of follow-up (28 days post-cardioversion plus 30 additional days), but we ensured adequate anticoagulation was administered by enoxaparin bridging to ensure no delays in cardioversion.
In this well-managed cohort of warfarin users with documented non-valvular AF in a clinical trial setting with a high TiTR (>70%), no difference was seen between TtTR and TiTR in relation to SAME-TT<sub>2</sub>R<sub>2</sub> score. Even in this short term study, TiTR was significantly related to bleeding events.

**Disclosures**

GYHL has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi Sankyo, and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi Sankyo. AG has served as a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer, and a speaker for Astra Zeneca, Bayer, Berlin Chemie, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Pfizer, and Sanofi-Aventis. NA-S and MS are employed by Covance, which received funding from Daiichi Sankyo for the management of the study. JJ, MM, SMW are employed by Daiichi Sankyo. DZ was employed by Daiichi Sankyo at the time the study was conducted.
References


Figure Legend

**Figure.** Efficacy and safety outcomes in relation to TiTR.

*Includes all patients from study sites where the mean TiTR of enoxaparin–warfarin patients was ≤70%.

†Includes all patients from study sites where the mean TiTR of enoxaparin–warfarin patients was >70%.

CRNM indicates clinically relevant non-major bleeding; CVD, cardiovascular death; MI, myocardial infarction; SEE, systemic embolic event; TiTR, time in therapeutic range.
Table 1. Clinical Characteristics of Patients Randomized to Enoxaparin–Warfarin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole Cohort (N=1104)</th>
<th>Oral Anticoagulant Naïve (n=296)</th>
<th>Oral Anticoagulant Experienced (n=808)</th>
<th>Oral Anticoagulant Naïve vs Experienced</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.2 ± 10.7</td>
<td>64.3 (10.8)</td>
<td>64.1 (10.8)</td>
<td>0.7782</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>382 (35%)</td>
<td>110 (37%)</td>
<td>272 (34%)</td>
<td>0.2790</td>
<td></td>
</tr>
<tr>
<td>CHA(2)DS(2)-VASc score</td>
<td>2.6 (1.4)</td>
<td>2.6 (1.4)</td>
<td>2.6 (1.4)</td>
<td>0.7666</td>
<td></td>
</tr>
<tr>
<td>HAS-BLED score</td>
<td>0.9 (0.8)</td>
<td>0.8 (0.8)</td>
<td>0.9 (0.8)</td>
<td>0.0416</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91.2 (19.0)</td>
<td>91.8 (19.0)</td>
<td>90.9 (19.0)</td>
<td>0.5189</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>94.1 (34.7)</td>
<td>97.5 (34.8)</td>
<td>92.9 (34.6)</td>
<td>0.0596</td>
<td></td>
</tr>
<tr>
<td>Time in therapeutic range (days)</td>
<td>59.8 (30.6)</td>
<td>54.4 (30.1)</td>
<td>61.8 (30.6)</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>SAMe-TT(2)R(2) score</td>
<td>2.1 (1.3)</td>
<td>2.0 (1.2)</td>
<td>2.2 (1.3)</td>
<td>0.0777</td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>63%</td>
<td>69%</td>
<td>61%</td>
<td>0.0176</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>37%</td>
<td>31%</td>
<td>39%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to achieve therapeutic range (days)</td>
<td>7.7 (5.1)</td>
<td>8.1 (4.5)</td>
<td>7.4 (5.4)</td>
<td>0.0662</td>
<td></td>
</tr>
<tr>
<td>Time in therapeutic range</td>
<td>70.8 (27%)</td>
<td>67.4 (29%)</td>
<td>72.0 (27%)</td>
<td>0.0204</td>
<td></td>
</tr>
</tbody>
</table>

*Calculated using the Rosendaal method.*
Values are mean (SD) unless otherwise specified.

*P*-values are based on two sample t-test and Chi-square test for continuous variables and categorical variables, respectively.
Table 2. Clinical Determinants of Time to Achieve Therapeutic range and Time in Therapeutic Range

<table>
<thead>
<tr>
<th>Clinical Factor</th>
<th>TtTR Coefficient</th>
<th>TtTR Estimate</th>
<th>TiTR Coefficient</th>
<th>TiTR Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.01 (0.03)</td>
<td>0.871</td>
<td>0.11 (0.15)</td>
<td>0.458</td>
</tr>
<tr>
<td>Women</td>
<td>-0.17 (0.52)</td>
<td>0.741</td>
<td>1.03 (2.33)</td>
<td>0.658</td>
</tr>
<tr>
<td>Non-white</td>
<td>0.97 (2.12)</td>
<td>0.647</td>
<td>0.29 (11.38)</td>
<td>0.980</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>-0.32 (0.52)</td>
<td>0.548</td>
<td>-1.23 (2.37)</td>
<td>0.604</td>
</tr>
<tr>
<td>Middle East &amp; Northern Africa</td>
<td>0.24 (1.03)</td>
<td>0.817</td>
<td>-6.66 (4.98)</td>
<td>0.181</td>
</tr>
<tr>
<td>North America</td>
<td>0.03 (0.99)</td>
<td>0.979</td>
<td>-8.77 (4.80)</td>
<td>0.068</td>
</tr>
<tr>
<td>Western. Europe</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>0.02 (0.01)</td>
<td>0.017</td>
<td>0.03 (0.04)</td>
<td>0.336</td>
</tr>
<tr>
<td>Cardioversion approach</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Transesophageal echocardiography</td>
<td>0.19 (0.42)</td>
<td>0.653</td>
<td>-2.41 (1.91)</td>
<td>0.207</td>
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<tr>
<td>Transesophageal echocardiography</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>Mean (SD)</td>
<td>Standard Error</td>
<td>Minimum (Maximum)</td>
<td>P-value</td>
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<tr>
<td>--------------------------</td>
<td>-----------</td>
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<td>---------</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.25 (1.95)</td>
<td>0.249</td>
<td>-9.79 (8.38)</td>
<td>0.243</td>
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<tr>
<td>Non-Hispanic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Anticoagulant experience</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experienced</td>
<td>-0.72 (0.43)</td>
<td>0.097</td>
<td>6.07 (2.16)</td>
<td>0.005</td>
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<td>Naive</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td><strong>CHA_{2}DS_{2}-VASc score</strong></td>
<td>-0.26 (0.23)</td>
<td>0.254</td>
<td>0.40 (1.04)</td>
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<td><strong>HAS-BLED score</strong></td>
<td>0.15 (0.35)</td>
<td>0.668</td>
<td>-3.66 (1.56)</td>
<td>0.019</td>
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<tr>
<td>Current smoker</td>
<td>0.24 (0.73)</td>
<td>0.745</td>
<td>4.26 (3.31)</td>
<td>0.199</td>
</tr>
<tr>
<td>Former smoker</td>
<td>-0.16 (0.53)</td>
<td>0.762</td>
<td>-0.47 (2.39)</td>
<td>0.843</td>
</tr>
<tr>
<td>Never smoker</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol use (drinks/day)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4.13 (2.97)</td>
<td>0.165</td>
<td>-11.36 (10.58)</td>
<td>0.283</td>
</tr>
<tr>
<td>&lt;1</td>
<td>4.66 (2.99)</td>
<td>0.119</td>
<td>-12.20 (10.62)</td>
<td>0.251</td>
</tr>
<tr>
<td>1–2</td>
<td>5.79 (3.06)</td>
<td>0.059</td>
<td>-13.11 (11.04)</td>
<td>0.235</td>
</tr>
<tr>
<td>&gt;2</td>
<td>2.74 (3.43)</td>
<td>0.424</td>
<td>-20.37 (13.20)</td>
<td>0.123</td>
</tr>
</tbody>
</table>

TiTR indicates time in therapeutic range; and TtTR, time to achieve therapeutic range.

Multivariate analysis is based on a linear model including covariates of age, gender, region, race, creatinine clearance, cardioversion approach, ethnicity, anticoagulant experience, CHA_{2}DS_{2}-VASc score, HAS-BLED score, smoking/tobacco use, and alcohol use.
Table 3. Relation of Time to Achieve Therapeutic Range and Time in Therapeutic Range to Efficacy and Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>TtTR ≤6</th>
<th>TtTR &gt;6</th>
<th>(95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/systemic embolic event/myocardial infarction/cardiovascular death</td>
<td>8/337 (2%)</td>
<td>2/358 (&lt;1%)</td>
<td>0.23 (0.02–1.17)</td>
<td>0.06</td>
</tr>
<tr>
<td>Any Bleeding</td>
<td>13/337 (4%)</td>
<td>10/358 (3%)</td>
<td>0.72 (0.28–1.80)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TiTR ≤70%</th>
<th>TiTR &gt;70%*</th>
<th>(95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/systemic embolic event/myocardial infarction/cardiovascular death</td>
<td>6/446 (1%)</td>
<td>3/528 (&lt;1%)</td>
<td>0.42 (0.07–1.98)</td>
<td>0.31</td>
</tr>
<tr>
<td>Any Bleeding</td>
<td>21/446 (5%)</td>
<td>10/528 (2%)</td>
<td>0.39 (0.16–0.88)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

TtTR indicates time to achieve therapeutic range; and TiTR, time in therapeutic range.

*Patient-based analysis.