

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)

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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-TT₂R₂ 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 CHA₂DS₂-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-TT₂R₂ 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-TT₂R₂ 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.¹ However, the effectiveness and safety of warfarin is dependent upon the quality of anticoagulation control (time in therapeutic range [TiTR])² even in the presence of a single stroke risk factor.³ Optimization of TiTR is dependent on many factors and the most common are included in the SAME-TT₂R₂ score.⁴ 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.⁵⁻⁸ 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.⁹ 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.^{9, 10} 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, TiTR, their clinical determinants and impact on efficacy and safety outcomes. For patients who had baseline INR <2.0 and reached INR \geq 2.0 during the on-treatment period, TtTR was defined as the first date of INR \geq 2.0 minus the date of first study drug administration. For patients who had $2.0 \geq$ INR \leq 3.0 during the on-treatment period, TiTR was defined as the percent of time in therapeutic range ($2.0 \geq$ INR \leq 3.0) from the first date of $2.0 \geq$ INR \leq 3.0.

Stroke and bleeding risk was defined by the CHA₂DS₂-VASC¹¹ and HAS-BLED¹² scores, respectively, while the SAME-TT₂R₂ score⁵ 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-TT₂R₂ 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 $\leq 70\%$ 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-TT₂R₂ score was not significantly different between the OAC experienced and naïve patients ($P=0.777$) but the proportion of patients with SAME-TT₂R₂ 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-TT₂R₂ score ≤ 2 and 259 (37%) had a SAME-TT₂R₂ score of >2. Mean TtTR in these SAME-TT₂R₂ 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-TT₂R₂ 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-TT₂R₂ 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.¹⁴ 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^{15,16} 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-TT₂R₂ score. Various studies have shown how the SAME-TT₂R₂ score can dichotomize those likely to do well on warfarin with a good TiTR (SAME-TT₂R₂ score 0-2) versus those less likely to achieve good TiTR (SAME-TT₂R₂ score >2).^{6,17} Furthermore, the validated SAME-TT₂R₂ score is predictive of labile INRs, as well as the adverse outcomes associated with poor anticoagulation control, such as thromboembolism, death and bleeding.⁸ Nonetheless, in this cohort with a high TiTR (>70%), the SAME-TT₂R₂ score did not discriminate between mean TtTR and TiTR. Similar findings were noted in another observational cohort with high TiTR,¹⁸ 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.²

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-TT₂R₂ 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

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–867.
2. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, Bankhead C, Xu Y. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes* 2008;1:84–91.
3. Proietti M, Lip GY. Major Outcomes in Atrial Fibrillation Patients with One Risk Factor: Impact of Time in Therapeutic Range Observations from the SPORTIF Trials. *Am J Med* 2016;129:1110–1116.
4. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAME-TT₂R₂ score. *Chest* 2013;144:1555–1563.
5. Proietti M, Lip GY. Simple decision making between a Vitamin K Antagonist and Non-Vitamin K Antagonist Oral Anticoagulant (NOACs): Using the SAME-TT₂R₂ Score. *Eur Heart J-Cardiovasc Pharmacother* 2015;1:150–152.
6. Ruiz-Ortiz M, Bertomeu V, Cequier A, Marin F, Anguita M. Validation of the SAME-TT₂R₂ score in a nationwide population of nonvalvular atrial fibrillation patients on vitamin K antagonists. *Thromb Haemost* 2015;114:695–701.
7. Fauchier L, Poli D, Olshansky B. The SAME-TT₂R₂ score and quality of anticoagulation in AF: Can we predict which patient benefits from anticoagulation? *Thromb Haemost* 2015;114:657–659.
8. Lip GY, Haguenoer K, Saint-Etienne C, Fauchier L. Relationship of the SAME-TT₂R₂ Score to Poor-Quality Anticoagulation, Stroke, Clinically Relevant Bleeding, and Mortality in Patients With Atrial Fibrillation. *Chest* 2014;146:719–726.
9. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR,

- Lip GY. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet* 2016;388:1995–2003.
10. Lip GY, Merino J, Ezekowitz M, Ellenbogen K, Zamoryakhin D, Lanz H, Jin J, Al-Saadi N, Mercuri M, Goette A. A prospective evaluation of edoxaban compared to warfarin in subjects undergoing cardioversion of atrial fibrillation: The Edoxaban vs. warfarin in subjects Undergoing cardioversion of Atrial Fibrillation (ENSURE-AF) study. *Am Heart J* 2015;169:597–604 e5.
 11. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263–272.
 12. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093–1100.
 13. Rosendaal FR, Cannegieter SC, van der Meer FJM, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;69:236–239.
 14. Proietti M, Lane DA, Lip GY. Chronic Kidney Disease, Time in Therapeutic Range and Adverse Clinical Outcomes in Anticoagulated Patients with Non-valvular Atrial Fibrillation: Observations from the SPORTIF Trials. *EBioMedicine* 2016;8:309–316.
 15. Clarkesmith DE, Pattison HM, Lip GY, Lane DA. Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomised trial. *PLoS One* 2013;8:e74037.
 16. Lip GY, Heinzel FR, Gaita F, Juanatey JR, Le Heuzey JY, Potpara T, Svendsen JH, Vos MA, Anker SD, Coats AJ, Haverkamp W, Manolis AS, Chung MK, Sanders P, Pieske B, Document R, Gorenek B, Lane D, Boriani G, Linde C, Hindricks G, Tsutsui H, Homma S, Brownstein S, Nielsen JC, Lainscak M, Crespo-Leiro M, Piepoli M, Seferovic P, Savelieva I. European Heart Rhythm Association/Heart Failure

Association joint consensus document on arrhythmias in heart failure, endorsed by –the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society. *Europace* 2016;18:12–36.

17. Bernaitis N, Ching CK, Chen L, Hon JS, Teo SC, Davey AK, Anoopkumar-Dukie S. The Sex, Age, Medical History, Treatment, Tobacco Use, Race Risk (SAME TT2R2) Score Predicts Warfarin Control in a Singaporean Population. *J Stroke Cerebrovasc Dis* 2017;26:64–69.
18. Skov J, Bladbjerg EM, Bor MV, Gram J. SAMeTT(2)R(2) does not predict time in therapeutic range of the international normalized ratio in patients attending a high-quality anticoagulation clinic. *Chest* 2014;145:187–188.
19. Esteve-Pastor MA, Roldan V, Valdes M, Lip GY, Marin F. The SAME-TT2R2 score and decision-making between a vitamin K antagonist or a non-vitamin K antagonist oral anticoagulant in patients with atrial fibrillation. *Expert Rev Cardiovasc Ther* 2016;14(2):177–187.
20. Pokorney SD, Simon DN, Thomas L, Gersh BJ, Hylek EM, Piccini JP, Peterson ED. Stability of International Normalized Ratios in Patients Taking Long-term Warfarin Therapy. *JAMA* 2016;316:661–663.

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 $\leq 70\%$.

† 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.

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Table 1. Clinical Characteristics of Patients Randomized to Enoxaparin–Warfarin

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

*Calculated using the Rosendaal method.¹³

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.

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Table 2. Clinical Determinants of Time to Achieve Therapeutic range and Time in Therapeutic Range

Clinical Factor	TtTR		TiTR	
	Coefficient Estimate (Standard Error)	<i>P</i> value	Coefficient Estimate (Standard Error)	<i>P</i> value
Age	0.01 (0.03)	0.871	0.11 (0.15)	0.458
Women	-0.17 (0.52)	0.741	1.03 (2.33)	0.658
Non-white	0.97 (2.12)	0.647	0.29 (11.38)	0.980
Eastern Europe	-0.32 (0.52)	0.548	-1.23 (2.37)	0.604
Middle East & Northern Africa	0.24 (1.03)	0.817	-6.66 (4.98)	0.181
North America	0.03 (0.99)	0.979	-8.77 (4.80)	0.068
Western. Europe	0		0	
Creatinine Clearance	0.02 (0.01)	0.017	0.03 (0.04)	0.336
Cardioversion approach				
Non-Transesophageal echocardiography	0.19 (0.42)	0.653	-2.41 (1.91)	0.207
Transesophageal echocardiography	0		0	

Hispanic	2.25 (1.95)	0.249	-9.79 (8.38)	0.243
Non-Hispanic	0		0	
Anticoagulant experience				
Experienced	-0.72 (0.43)	0.097	6.07 (2.16)	0.005
Naive	0		0	
CHA ₂ DS ₂ -VASc score	-0.26 (0.23)	0.254	0.40 (1.04)	0.702
HAS-BLED score	0.15 (0.35)	0.668	-3.66 (1.56)	0.019
Current smoker	0.24 (0.73)	0.745	4.26 (3.31)	0.199
Former smoker	-0.16 (0.53)	0.762	-0.47 (2.39)	0.843
Never smoker	0		0	
Alcohol use (drinks/day)				
None	4.13 (2.97)	0.165	-11.36 (10.58)	0.283
<1	4.66 (2.99)	0.119	-12.20 (10.62)	0.251
1–2	5.79 (3.06)	0.059	-13.11 (11.04)	0.235
>2	2.74 (3.43)	0.424	-20.37 (13.20)	0.123

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, CHA₂DS₂-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

	TtTR ≤6	TtTR >6	Odds Ratio (95% CI)	P-value
Stroke/systemic embolic event/myocardial infarction/cardiovascular death	8/337 (2%)	2/358 (<1%)	0.23 (0.02–1.17)	0.06
Any Bleeding	13/337 (4%)	10/358 (3%)	0.72 (0.28–1.80)	0.53
	TiTR ≤70%	TiTR >70%*	Odds Ratio (95% CI)	P-value
Stroke/systemic embolic event/myocardial infarction/cardiovascular death	6/446 (1%)	3/528 (<1%)	0.42 (0.07–1.98)	0.31
Any Bleeding	21/446 (5%)	10/528 (2%)	0.39 (0.16–0.88)	0.02

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

*Patient-based analysis.