

Comparison of Outcomes Among Patients Randomized to Warfarin Therapy According to Anticoagulant Control

Results From SPORTIF III and V

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Background: Warfarin sodium reduces stroke risk in patients with atrial fibrillation, but international normalized ratio (INR) monitoring is required. Target INRs are frequently not achieved, and the risk of death, bleeding, myocardial infarction (MI), and stroke or systemic embolism event (SEE) may be related to INR control.

Methods: We analyzed the relationship between INR control and the rates of death, bleeding, MI, and stroke or SEE among 3587 patients with atrial fibrillation randomized to receive warfarin treatment in the SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) III and V trials. The mean±SD follow-up was 16.6±6.3 months. Patients were divided into 3 equal groups (those with good control [$>75\%$], those with moderate control [$60\%-75\%$], or those with poor control [$<60\%$]) according to the percentage time with an INR of 2.0 to 3.0. Outcomes were compared

according to INR control. The main outcome measures were death, bleeding, MI, and stroke or SEE.

Results: The poor control group had higher rates of annual mortality (4.20%) and major bleeding (3.85%) compared with the moderate control group (1.84% and 1.96%, respectively) and the good control group (1.69% and 1.58%, respectively) ($P<.01$ for all). Compared with the good control group, the poor control group had higher rates of MI (1.38% vs 0.62%, $P=.04$) and of stroke or SEE (2.10% vs 1.07%, $P=.02$).

Conclusions: In patients with atrial fibrillation taking warfarin, the risks of death, MI, major bleeding, and stroke or SEE are related to INR control. Good INR control is important to improve patient outcomes.

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IN PATIENTS WITH ATRIAL FIBRILLATION (AF), the use of warfarin sodium compared with placebo has been shown to prevent the composite of ischemic stroke and hemorrhagic stroke by 62% and is the standard treatment.¹ However, warfarin therapy has several drawbacks, including the requirement of close coagulation monitoring of the international normalized ratio (INR) and interactions with various foods and drugs.² Subtherapeutic intensities of anticoagulation can lead to a high stroke risk, and excessive anticoagulation results in higher rates of major bleeding, including intracranial hemorrhage.³

*See also pages 229
and 246*

In the SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) III trial,⁴ 3410 patients were

randomized to receive a fixed dosage of the oral direct thrombin inhibitor ximelagatran or adjusted-dose warfarin in an open-label fashion. In a similar but double-blind study, the SPORTIF V trial, 3922 patients were randomized to receive ximelagatran or warfarin.⁵ Patients with AF and at least 1 additional risk factor for stroke were enrolled in these trials, and the primary analysis in each study compared the efficacy of the randomized treatments for the reduction of stroke or systemic embolism event (SEE) rates. The dosage of warfarin was adjusted at least every 30 days, aiming to maintain the INR between 2.0 and 3.0.

The SPORTIF III trial showed that ximelagatran was not inferior to warfarin relative to the outcome of annual rates of stroke or SEE (1.6% with ximelagatran vs 2.3% with warfarin)⁴; the SPORTIF V trial also showed that ximelagatran was not inferior to warfarin therapy (1.6% with

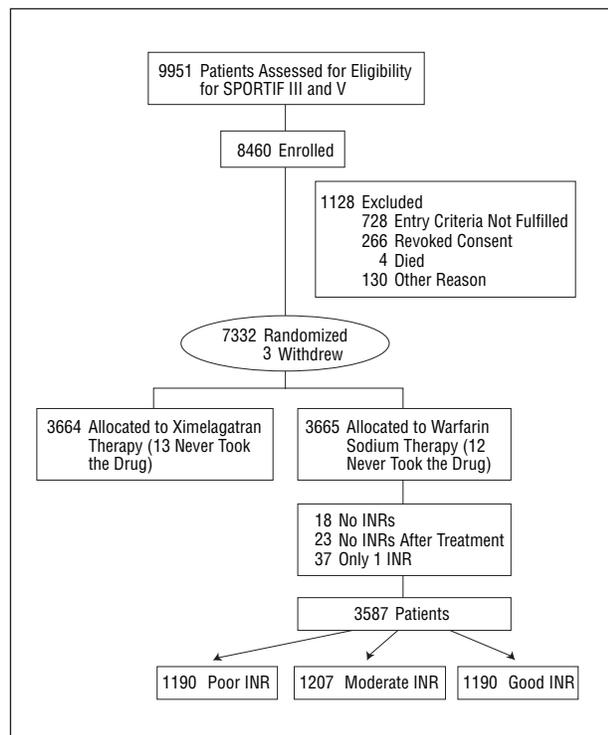


Figure. Patient flowchart. INR indicates international normalized ratio; SPORTIF, Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation.

ximelagatran vs 1.2% with warfarin).⁵ The trials showed no difference in major bleeding, but the combination of major and minor bleeding was less frequent in those participants who received ximelagatran.⁶

In this study, we combined data from the SPORTIF III and V trials. We analyzed the relationship between INR control and the rates of death, bleeding, stroke or SEE, and myocardial infarction (MI) among patients randomized to receive warfarin.

METHODS

The design, rationale, and primary results of the SPORTIF III and V trials have been published.^{4,6} Both trials compared oral ximelagatran (36 mg twice daily) with adjusted-dose warfarin for prevention of stroke and SEE in moderate-risk to high-risk patients with AF. Written consent was required from each patient according to a protocol approved by local institutional review boards and compliant with the Declaration of Helsinki. Patients required at least 1 of the following risk factors in addition to having persistent or paroxysmal AF: (1) previous stroke, SEE, or transient ischemic attack (TIA), (2) hypertension and left ventricular dysfunction (ejection fraction <40% or symptomatic systolic or diastolic heart failure), or (3) 75 years or older, or 65 years or older with known coronary disease or diabetes mellitus. The SPORTIF III trial was an international randomized, multicenter, open-label, parallel-group trial carried out in 23 countries. The SPORTIF V trial was an identical but double-blind trial carried out in Canada and the United States. It was prespecified that a combined study of these 2 trials would be performed and that outcomes would be analyzed according to INR control.

For patients randomized to receive warfarin, INR measurements were performed at least monthly, and warfarin dosages were adjusted to achieve an INR between 2.0 and

3.0. If the INR was out of the therapeutic range or if there had been a change in diet, other medications, or medical condition, the INR was checked more frequently. The protocol specified that patients were to be withdrawn after a primary event. Patients were continued in the study with subsequent INR measurements if bleeding or MI occurred. Concomitant aspirin therapy (<100 mg/d) was allowed, and patients were stratified at randomization based on whether they were taking aspirin.

END POINT DEFINITIONS

Events

The following 4 end point definitions were: (1) stroke: abrupt onset of a focal neurological deficit in the distribution of a brain artery persisting ≥ 24 hours or due to intracerebral hemorrhage, (2) transient ischemic attack: abrupt onset of a focal neurological deficit in the distribution of a brain artery persisting longer than 24 hours, (3) systemic embolic event: abrupt vascular insufficiency associated with clinical and radiological evidence of arterial occlusion in the absence of another likely mechanism, and (4) myocardial infarction: 2 or more of the following¹: typical chest pain for 20 minutes or longer,² electrocardiogram showing changes of MI, or cardiac enzyme elevation greater than 2 times the upper limit of normal.³

Bleeding

Major bleeding was defined as fatal bleeding, clinically overt blood loss requiring transfusion of 2 U or more, clinically overt bleeding associated with a reduction in hemoglobin level of 2.0 g/dL or more, or bleeding involving critical anatomical sites (ie, subdural hematoma, intraspinal hemorrhage, intraocular hemorrhage, retroperitoneal hemorrhage, pericardial hemorrhage, or atraumatic intraarticular hemorrhage). Hemorrhagic strokes were considered separately. Minor bleeding was defined as other bleeding not fulfilling the criteria for major bleeding, including bleeding precipitating treatment cessation.

STATISTICAL ANALYSIS

For this analysis, we determined the percentage time each patient assigned to warfarin therapy was in the therapeutic range during the study. A daily INR was calculated based on linear interpolation using the slope of all actual measured INR values allotted during the trial.⁷ After the slope was calculated, a value was substituted for each day the patient was taking study medication but did not have an actual INR measurement. We did not limit the amount of time between INR measurements for inclusion in our interpretation calculations. Patients randomized to warfarin were then categorized into 3 groups based on the percentage time they spent in the therapeutic range (INR, 2.0-3.0). We defined good control as the one third of patients who spent the most time in the 2.0- to 3.0-INR range, poor control as the one third who spent the most time out of the 2.0- to 3.0-INR range, and moderate control as the one third who achieved an intermediate level of INR control. The original combined sample consisted of 3665 patients randomized to warfarin (**Figure**). After excluding 18 patients with no INR measurements, 23 patients with no INR measurements after treatment, and 37 patients with only 1 INR measurement after treatment, there were 3587 patients remaining.

Covariates for models were chosen based on significance of differences between baseline characteristics by INR control.

Table 1. Baseline Characteristics of Patients According to International Normalized Ratio (INR) Control*

Characteristic	Poor Control† (n = 1190)	Moderate Control‡ (n = 1207)	Good Control§ (n = 1190)	P Value
Male sex	68.7	68.7	71.8	.16
Age, y	70.8 (9.3)	70.8 (8.7)	71.1 (8.4)	.70
Body mass index¶	28.5 (5.6)	29.2 (5.9)	29.0 (5.5)	.02
Body weight, kg	83.5 (19.9)	86.7 (20.6)	87.0 (18.8)	<.001
Race/ethnicity				<.001
White	87.3	93.7	96.1	
Asian	9.6	4.5	3.0	
Black/African American	2.5	1.6	0.8	
Other	0.6	0.2	0.0	
Aspirin use during ≥50% of the time while taking the study drug	14.5	13.4	11.8	.17
Vitamin K antagonist use at study entry	70.8	81.9	85.0	<.001
Blood pressure, mm Hg				
Systolic	134.9 (18.0)	135.3 (18.1)	135.8 (18.2)	.43
Diastolic	79.1 (10.6)	79.1 (10.7)	80.0 (10.1)	.05
AF onset within 1 y	21.9	17.5	18.5	.03
Paroxysmal AF type	13.0	10.8	7.8	<.001
Risk factors#				.11
1	28.5	30.1	29.1	
2	30.3	29.6	35.7	
≥3	41.2	40.3	35.2	
Previous stroke, transient ischemic attack, or both	21.8	21.5	18.1	.04
Previous systemic embolism	4.5	4.2	4.3	.92
Age >75 y	38.2	36.3	38.2	.54
Hypertension	78.5	76.5	75.0	.12
Left ventricular dysfunction	37.9	38.6	35.6	.29
Age ≥65 y and coronary heart disease	36.9	37.3	37.2	.98
Age ≥65 y and diabetes mellitus	19.2	18.0	16.5	.23

Abbreviation: AF, atrial fibrillation.

*Data are given as percentage or as mean (SD).

†Therapeutic INR range less than 60% of the time.

‡Therapeutic INR range 60% to 75% of the time.

§Therapeutic INR range more than 75% of the time.

||P values for categorical variables are based on Pearson product moment correlation χ^2 test, and P values for continuous variables are based on Kruskal-Wallis test.

¶Calculated as weight in kilograms divided by height in meters squared.

#For risk factors, see the "Methods" section.

Kruskal-Wallis tests were used for continuous variables, and Pearson product moment correlation χ^2 tests were used for categorical variables. The significant covariates included in modeling were age, body mass index (calculated as weight in kilograms divided by height in meters squared), race/ethnicity, trial (SPORTIF III or V), INR control status, diastolic blood pressure, previous stroke or TIA, AF type (paroxysmal or persistent), vitamin K antagonist use at study enrollment, and aspirin use at least 50% of the time while taking the study drug. Data on onset of AF within 1 year were missing for 9% of the patients and were not included in multivariate modeling. The proportionality assumption was checked for all covariates by including time-dependent terms. If these terms were significant at $P < .05$, they were included in the overall model along with the covariates listed.

Of the 3587 patients, 21 had missing covariate values, leaving a sample of 3566 patients available for multivariate analyses. An on-treatment analysis, defined as patients receiving randomized treatment, was used to achieve the most accurate assessment of risks associated with different intensities of warfarin therapy. Cox proportional hazards models were used for multivariate analysis of time to event. Because of the exploratory nature of these analyses, no statistical adjustments were made for the multiplicity of analyses performed.

RESULTS

The mean \pm SD duration of follow-up was 16.6 ± 6.3 months. The time between INR measurements was 57 days or less in 99% of patients and 36 days or less in 95% of patients. The median number of INR measurements was 23 in the good control group, 24 in the moderate control group, and 21 in the poor control group. In the good control group, 1190 patients had an INR in the therapeutic range more than 75% (median, 83%) of the time. In the moderate control group, 1207 patients had an INR in the therapeutic range 60% to 75% (median, 68%) of the time. In the poor control group, 1190 patients had an INR in the therapeutic range less than 60% (median, 48%) of the time.

Baseline demographics of the groups are given in **Table 1**. Compared with patients in the moderate and good control groups, patients in the poor control group had lower body weight, were less likely to be taking a vitamin K antagonist, and were more likely to have paroxysmal AF, be of Asian race/ethnicity, and be taking aspirin before randomization.

Table 2. Ischemic Events per 100 Patient-Years and Bleeding According to International Normalized Ratio Control*

Ischemic Event	Poor Control Group (n = 1190)	P Value (Poor vs Good)	Moderate Control Group (n = 1207)	P Value (Moderate vs Poor)	Good Control Group (n = 1190)	P Value (Good vs Moderate)
Stroke or systemic embolism	2.10	.02	1.34	.09	1.07	.48
Ischemic stroke	1.84	.06	1.06	.06	1.02	.91
Hemorrhagic stroke	0.20	.26	0.28	.64	0.06	.11
Systemic embolism	0.07	.29	0.06	.88	0.00	.31
Transient ischemic attack	0.53	.03	1.01	.10	1.20	.60
Myocardial infarction	1.38	.04	0.89	.22	0.62	.35
Death, all cause	4.20	<.01	1.84	<.01	1.69	.74
Death, stroke, or systemic embolism	5.98	<.01	3.01	<.01	2.76	.67
Death, stroke, systemic embolism, or major bleeding	9.32	<.01	4.89	<.01	4.31	.41
Major bleeding†	3.85	<.01	1.96	<.01	1.58	.38
Major or minor bleeding	43.64	<.01	41.81	.91	34.05	<.01

*P values are based on the log rank test. Results for end points with low event rates should be interpreted with caution.

†Excluding hemorrhagic stroke.

Table 3. Ischemic Events per 100 Patient-Years and Bleeding According to International Normalized Ratio Control and Aspirin Use During the Study*

Ischemic Event	Poor Control Group (n = 1190)		Moderate Control Group (n = 1207)		Good Control Group (n = 1190)	
	Aspirin (n = 172)	No Aspirin (n = 1018)	Aspirin (n = 162)	No Aspirin (n = 1045)	Aspirin (n = 141)	No Aspirin (n = 1049)
Stroke or systemic embolism	2.01	2.12	0.83	1.42	1.97	0.96
Myocardial infarction	2.02	1.29	0.42	0.97	0	0.70
Death, all cause	3.52	4.30	2.92	1.67	1.47	1.72
Major bleeding	5.05	3.67	4.26†	1.61†	2.46	1.47

*Aspirin use during the study was defined as a patient's use of aspirin at least 50% of the time while taking the study drug.

†Significantly different ($P = .007$, log rank test). Results for end points with low event rates should be interpreted with caution.

OUTCOMES ACCORDING TO INR CONTROL

Table 2 gives outcomes according to INR control, with 43% (32/75) of events occurring in the poor control group. The poor control group had higher rates of annual mortality (4.20%) and major bleeding (3.85%) compared with the moderate control group (1.84% and 1.96%, respectively) and the good control group (1.69% and 1.58%, respectively) ($P < .01$ for all). Compared with the good control group, the poor control group had higher rates of MI (1.38% vs 0.62%, $P = .04$) and of stroke or SEE (2.10% vs 1.07%, $P = .02$). Transient ischemic attacks were less frequent in the poor control group.

OUTCOMES ACCORDING TO STABILITY OF INR CONTROL

Of 1148 patients with good INR control in the first 6 months, 54.5% remained in this category, 27.7% moved to the moderate control category, and 17.8% moved to the poor control category for the rest of the study. Of 844 patients with moderate control in the first 6 months, 32.4% remained in this category, 28.2% moved to the poor control category, and 39.5% moved to the good control category for the rest of the study. Of 1233 patients with poor

control in the first 6 months, 44.2% remained in this category, 29.3% moved to the moderate control category, and 26.5% moved to the good control category for the rest of the study.

In all 3 subgroups, the 6-month INR control was associated with INR control for the remainder of the study. Patients in the poor control group had the highest chance of being in the poor control group for the rest of the study.

BLEEDING ACCORDING TO INR CONTROL

Major bleeding rates were lower with moderate and good INR control compared with poor INR control ($P < .01$). All bleeds (major and minor combined) were less frequent with good INR control compared with moderate or poor INR control ($P < .01$).

EFFECT OF ASPIRIN USE

There were 3587 patients taking aspirin; 56% were older than 65 years and had coronary heart disease, and 20% were older than 65 years and had diabetes mellitus. **Table 3** summarizes the ischemic events and bleeding, with and without aspirin use, during the study. There were no differences in rates of death, MI,

Table 4. Multivariate Adjustment of Ischemic Events and Bleeding in the Moderate Control Group and the Good Control Group*

Variable	Moderate Control Group	P Value†	Good Control Group	P Value‡
Stroke or systemic embolism	0.68 (0.40-1.17)	.16	0.54 (0.30-0.97)	.04
Ischemic stroke	0.60 (0.33-1.08)	.08	0.57 (0.31-1.04)	.07
Transient ischemic attack	1.85 (0.80-4.29)	.15	2.30 (1.01-5.26)	.05
Myocardial infarction	0.58 (0.30-1.12)	.10	0.44 (0.21-0.93)	.03
Death, all cause	0.42 (0.27-0.64)	<.001	0.41 (0.26-0.64)	<.001
Death, stroke, or systemic embolism	0.50 (0.36-0.71)	<.001	0.48 (0.34-0.68)	<.001
Death, stroke, systemic embolism, or major bleeding	0.52 (0.39-0.68)	<.001	0.47 (0.36-0.63)	<.001

*Data are given as hazard ratio (95% confidence interval) unless otherwise indicated. Because of missing values for covariates included in the models, there were 1182, 1204, and 1180 patients in the good, moderate, and poor control groups, respectively.

†Compared with the poor control group from Cox proportional hazards regression models, adjusting for age, body mass index, race/ethnicity, trial (SPORTIF [Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation] III or V), international normalized ratio control status, diastolic blood pressure, previous stroke or transient ischemic attack, paroxysmal atrial fibrillation type, vitamin K antagonist use at study entry, and aspirin use at least 50% of the time while taking the study drug.

and stroke or SEE, but major bleeding was significantly increased among patients taking warfarin with moderate INR control and concomitant aspirin therapy compared with patients with moderate INR control and no aspirin therapy ($P=.007$).

ADJUSTED OUTCOMES ACCORDING TO INR CONTROL

Table 4 gives the adjusted hazard ratios of the moderate and good control groups compared with the poor control group. Rates of stroke or SEE were higher among patients with poor INR control compared with patients with good INR control ($P=.04$). Total mortality was higher with poor INR control compared with moderate INR control and good INR control ($P<.001$ for both). Poor INR control was associated with an increased incidence of MI (poor control vs good control, $P=.03$) but with a decreased incidence of TIA (poor control vs good control, $P=.05$).

COMMENT

This study demonstrates that INR control with warfarin therapy is variable even in the context of carefully conducted clinical trials with strict enrollment and exclusion criteria and mandated follow-up with regular INR measurements. Patients with poor INR control had more than 2% per patient-year higher absolute total mortality compared with patients with good INR control or patients with moderate INR control, despite having rigorous management in the context of a clinical trial. The rates of the primary events of stroke or SEE, as well as the bleeding rates, were higher among patients with poor INR control compared with those among patients with moderate and good INR control. The rates of MI were significantly higher among patients with poor control compared with those among patients with good INR control. The novel finding of a reduction in mortality associated with better INR control can be explained by the decreased rates of stroke and MI with better INR control. Aspirin therapy had no major effect on event rates relative to INR control but increased bleeding in the patients with moderate INR control.

The development of the comparator ximelagatran in the SPORTIF trials was stopped because of risk of severe toxic effects to the liver. Transient elevation of liver enzymes occurred in 6.1% of patients in the SPORTIF trials.⁸ Comparisons of INR control with outcomes of ximelagatran therapy are not included in this analysis.

In our study, the incidence of TIA was higher among patients with good INR control compared with that among patients with poor INR control. In the poor control group, there were significantly more patients who had onset of AF within 1 year and more patients who had paroxysmal AF; patients in the poor control group may have been exposed for a shorter time to the risk of AF, stroke, and TIA. Also it may be that good INR control led to smaller emboli that resulted in TIAs rather than strokes and, therefore, there were fewer strokes but more TIAs among patients with good INR control, which was not the case for patients with poor INR control. Hence, more TIAs may represent a positive treatment effect when analyzed together with the reduction in the incidence of ischemic strokes associated with good INR control. This observation is compatible with the findings of a retrospective study⁹ of patients with AF; in 188 patients who experienced stroke, there was greater disability as assessed by the modified Rankin Scale and higher 30-day mortality when the INR on admission was less than 2.0 vs 2.0 or higher.

In patients with nonvalvular AF who are prescribed warfarin, it is generally recommended that the target INR should be between 2.0 and 3.0.^{3,9} However, only about 50% of patients at high risk of stroke in the community are prescribed warfarin.¹⁰⁻¹³ Outside of a trial setting, the INR control of these patients is often less than optimal and is not as good as that achieved in the SPORTIF trials. In community practice, INR control within a range of 2.0 to 3.0 is typically achieved in about 50% of measurements,^{10,14,15} with patients with low INR control being at risk of stroke¹⁶ and patients with high INR control being at risk of hemorrhage.¹⁷

In the SPORTIF trials, INRs were in the therapeutic range of 2.0 to 3.0 67.5% of the time. We analyzed whether INR control in the first 6 months predicted

subsequent INR control. The 6-month INR control was associated with INR control for the rest of the study, and patients in the poor control group had the highest chance of continuing to have poor INR control. Our data are similar to previous findings demonstrating that INR control in the first 30 days is predictive of subsequent INR control.¹⁸ We chose a longer 6-month initial assessment period of INR control. Patients with poor INR control at 6 months are likely to have poor INR control in the long term, prompting institution of more intensive monitoring.

Myocardial infarction, as defined by the old World Health Organization criteria,¹⁹ was reduced by 56% (hazard ratio, 0.44; 95% confidence interval, 0.21-0.93) after multivariate adjustment in our study. Among a population with AF taking warfarin, the prevention of MI relative to INR control has not been previously reported, to our knowledge. Whether using the new joint European Society of Cardiology and American College of Cardiology definition of MI,²⁰ which stresses the use of troponins for the diagnosis of MI, would show greater benefit with better INR control is unknown.

There are several limitations to this study. We performed multiple comparisons and did not adjust for multiple testing. This analysis combines results from a double-blind trial⁵ with those from an open-label trial,⁴ with different event rates. However, multivariate analysis showed that trial status was not a significant factor for the determination of risk and benefit according to INR control. In SPORTIF V, point-of-care devices and a core laboratory were used, whereas local laboratories were used in SPORTIF III. The classification into the 3 groups of poor, moderate, and good INR control was arbitrary. We cannot determine if the increase in adverse outcomes was caused by poor INR control or if poor INR control is a marker for other comorbidities that were responsible for the worse outcomes. Varying lengths of times of observation (because of increased mortality rates among patients with poor INR control) could have affected the incidence of nonfatal events, as well as the fact that physicians may increase the intensity of INR monitoring following an event. Finally, although this post hoc analysis was prespecified, the investigations were not statistically powered to show differences between various classifications of INR control.

In conclusion, our prespecified post hoc analysis demonstrates that, even in the context of clinical trials with rigorous follow-up, two thirds of patients receiving warfarin have therapeutic INRs between 2.0 and 3.0 75% of the time or less. Patients with poor INR control had increased rates of death, bleeding, MI, and stroke or SEE compared with patients with good INR control. Assiduous INR control with warfarin administration is likely to lead to better patient outcomes.

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Author Contributions: Dr White had complete access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* White and Albers. *Acquisition of data:* White, Kaatz, Tse, and Albers. *Analysis and interpretation of data:* White, Gruber, Feyzi, Kaatz, Tse, Husted, and Albers. *Drafting of the manuscript:* White. *Critical revision of the manuscript for important intellectual content:* Feyzi, Kaatz, Tse, Husted, and Albers. *Statistical analysis:* Gruber and Feyzi.

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