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Quality of Anticoagulation Control in Preventing Adverse Events in Heart Failure Patients in Sinus Rhythm: A Warfarin Aspirin Reduced Cardiac Ejection Fraction Trial (WARCEF) Substudy

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Please see the Supplemental Material for a full list of WARCEF investigators

Disclosures

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Abstract

Background—The aim of this study is to examine the relationship between time in therapeutic range (TTR) and clinical outcomes in heart failure (HF) patients in sinus rhythm (SR) treated with warfarin.

Methods and Results—We used data from the Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction Trial (WARCEF) to assess the relationship of TTR with the WARCEF primary outcome (ischemic stroke, intracerebral hemorrhage, or death); with death alone; ischemic stroke alone; major hemorrhage alone; and net clinical benefit (primary outcome and major hemorrhage combined). Multivariable Cox models were used to examine how the event risk changed with TTR and to compare the high TTR, low TTR, and aspirin patients, with TTR being treated as a time-dependent covariate. 2,217 patients were included in the analyses, among whom 1,067 were randomized to warfarin and 1,150 were randomized to aspirin. The median (IQR) follow-up duration was 3.6 (2.0–5.0) years. Mean (±SD) age was 61±11.3 years, with 80% being men. The mean (±SD) TTR was 57% (±28.5%). Increasing TTR was significantly associated with reduction in primary outcome (adjusted $p<0.001$), death alone (adjusted $p=0.001$), and improved net clinical benefit (adjusted $p<0.001$). A similar trend was observed for the other two outcomes but significance was not reached (adjusted $p=0.082$ for ischemic stroke, adjusted $p=0.109$ for major hemorrhage).

Conclusions—In HF patients in SR, increasing TTR is associated with better outcome and improved net clinical benefit. Patients in whom good quality anticoagulation can be achieved may benefit from the use of anticoagulants.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00041938.

Keywords

heart failure; anticoagulant; stroke; hemorrhage

Anticoagulation with warfarin is widely used to prevent stroke and other thromboembolic events. Efficacy and safety of vitamin K antagonists such as warfarin is dependent upon the quality of anticoagulation control as reflected by the average time each patient spends in therapeutic range (TTR). With a high TTR, thromboembolic and bleeding risks are reduced. (1–6) As such, TTR is considered a major factor in reducing adverse events in anticoagulated patients treated with warfarin. However, the impact of TTR on warfarin treated patients with heart failure (HF) in sinus rhythm (SR) is not known, and no previous study has assessed this issue. This question is particularly important when considering the potential of evaluating the role of newer, non-vitamin K antagonist oral anticoagulants in preventing adverse events in patients with HF.

The Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial was the largest double-blind randomized study of HF patients in SR treated with warfarin or aspirin.(7) It showed that although ischemic stroke was reduced by the use of warfarin, the primary endpoint of stroke (ischemic and hemorrhagic) or death combined did not differ between the two arms. Warfarin use was also associated with increased bleeding. We hypothesized that outcome events and bleeding in those receiving warfarin may have been influenced by the level of TTR achieved. As such, in the current ancillary analysis, we tested this hypothesis by examining the relationship of TTR and event rates. Additionally, we explored the major hemorrhage rate in relation to TTR in HF patients. As far as we are aware, this is the first study to assess warfarin effectiveness and bleeding rate classified by TTR in HF patients in SR.

Methods

WARCEF

This analysis used information obtained in the double-blind WARCEF trial (http://www.ClinicalTrials.govNo.NCT00041938), in which patients with left ventricular ejection fraction (LVEF) ≤35% in SR were randomly assigned to warfarin (target INR 2.75, with acceptable INR range of 2.0 to 3.5) or aspirin (325 mg per day). The design has been previously reported.(7) The primary efficacy outcome was time to the first occurrence of stroke (ischemic or hemorrhagic) or death. Major hemorrhage was defined as intracerebral, epidural, subdural, subarachnoid, spinal intramedullary, retinal hemorrhage, any other bleeding with more than 2 gm hemoglobin decline in 48 hours, those requiring two units or more of transfusion, or requiring hospitalization or surgical intervention. The study was approved by Institutional Review Boards at the coordinating centers for all sites, and all subjects provided informed consent.

Analysis

To assess TTR, daily international normalized ratios (INRs) were imputed. We assumed that any change between two consecutive INR measurements takes place linearly over a 5-day period. For the time period between two consecutive INR measurements, we imputed INR backwards using the INR value of the second measurement till 5 days after the first measurement. Then we imputed the first 5 days using linear interpolation of these two INR values.(8) A six-weeks initial titration phase is allowed when calculating TTR. At each time point, TTR for each patient is the up-to-date percentage of time on study medication from the 7^{th} week for which the patient was in therapeutic range (INR of 2 to 3.5). The final TTR for each patient is the patient's TTR at the end of follow up. Seventy-five warfarin patients either had follow up time less than 6 weeks or were on interruption of therapy (IOT) after 6 weeks, and thus have missing TTR throughout the study. These patients were excluded from the analyses. To allow for a fair comparison, 13 aspirin patients with follow up time less than 6 weeks were also excluded, giving a total sample of 2,217 patients.

We divided warfarin-treated patients into two groups, the high TTR group (final TTR≥60%) and the low TTR (final TTR<60%) group; the cut-point of 60% yields a similar sample size in each group. Clinical and laboratory variables, as well as adverse events, were compared

among these two groups and aspirin patients using an ANOVA F-test for continuous variables, Chi-squared test for categorical variables, and log-rank test for time-to-event outcomes.

Cox models in which TTR was treated as a time-dependent covariate were used to assess the impact of TTR on the primary outcome, on death alone, on ischemic stroke alone, and on major hemorrhage among all warfarin-treated patients. Net clinical benefit was assessed by combining the primary outcome and major hemorrhage.

We also compared risk of the primary outcome among the high TTR group (TTR≥60%), the low TTR group (TTR<60%) and the aspirin treated patients using a Cox model, in which the TTR groups were time-dependent, i.e., they changed over time based on the value of the up-to-date TTR value for each patient.

All the analyses were stratified by continent, taking advantage of the fact that randomization in WARCEF was stratified by site and therefore by continent. To address the possibility that better TTR may be a proxy for better baseline health and/or better health awareness and access to medical care, we considered all baseline characteristics listed in Table 1, and adjusted the above analyses for variables that were significantly associated with each outcome by using stepwise forward-backward selection, with entry and removal criteria of p=0.05. P-values for the regression coefficients and 95% CI were calculated based on the Wald test. Missing values were imputed using means for continuous variables and modal values for categorical variables. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

Results

Of the 2,217 patients, 1,067 were randomized to warfarin and 1,150 patients to aspirin. Overall median (IQR) follow-up was 3.6 (2.0–5.0) years. Descriptive statistics for patient variables and adverse events are shown in Table 1. Overall, 71,461 INRs were analysed in five laboratories that represented geographic locations of the study sites (North America, South America and three locations in Europe). The mean (±SD) final TTR per patient was 57% (±28.5%) for warfarin patients, lower than the overall proportion of TTR reported in the primary WARCEF manuscript because patients with shorter times on warfarin had lower TTRs.[7] When patients were not in therapeutic range, on average, more time was spent below therapeutic range (32.4%±28.9%) than above (10.5%±12.9%).

Results showing the impact of time-dependent TTR on time-to-event outcomes are presented in Table 2. In three of the five outcomes of interest, the event risk declined significantly as TTR increased. For every 10% increase in TTR, the adjusted hazard ratio (aHR) for the primary outcome was 0.92 (p<0.001), and the aHR for death was 0.93 (p=0.001). For ischemic stroke alone, the aHR of event was 0.88 for every 10% increase in TTR, but did not reach significance (p=0.082). Similarly, for major hemorrhage, the aHR of event was 0.93 (p=0.109). For net benefit of warfarin, which combines the primary composite event and major hemorrhage, the aHR was 0.91 for every 10% increase in TTR

(p<0.001). We also tested for the effect of TTR when it was limited to 2 to 3 as a sensitivity analysis, and observed similar results (data not shown).

A time-dependent comparison of primary outcome risk among the high TTR, low TTR, and aspirin groups is presented in Table 3. Those with high TTRs at any time were at less risk of an event than both those with lower TTRs at any time (aHR=0.74, p=0.015) and those in the aspirin group (aHR=0.76, p=0.010), while the low TTR group experienced similar risk as the aspirin group (aHR=1.03, p=0.790).

Discussion

In this study, we show for the first time that in HF patients in SR, increasing TTR is associated with better outcomes and improved net clinical benefit. High TTR patients fared better than low TTR patients and those receiving aspirin. On the other hand, patients with low TTR tended to do similarly compared to patients receiving aspirin, implying that high quality anticoagulation with warfarin, or potentially the use of newer oral anticoagulants may be better than aspirin in preventing adverse outcomes.

In patients with atrial fibrillation (AF), the efficacy of vitamin K antagonists such as warfarin in preventing adverse events depends on the individual patient's TTR.(1–4) A higher TTR is associated with a lower event probability. It is also shown that in other clinical situations in which anticoagulation is indicated, the event rate declines as TTR increases.(5,6)

In our analysis of WARCEF data, the lower event rates with high TTR was observed for primary event, death alone, and for net clinical benefit. There was a trend towards better stroke outcomes with high TTR but this did not reach statistical significance. High TTR patients also did better compared with aspirin treated patients. Although WARCEF lacked a placebo group, the increasing effectiveness of warfarin as TTR increases is consistent with a potential benefit of warfarin in HF if the quality of anticoagulation control was good. Patients with HF, particularly those with reduced EF, are at increased risk for cardiovascular death.(9) It has been shown that cardiac events may be due to microembolization.(10) It is possible that such events were prevented in our study by the use of warfarin, thus leading to lower rate of death. It is also known that patients with HF tend to develop atrial fibrillation. (11) As such, it is possible that transient AF may have developed in our patients, as has been noted in patients with unknown cause of stroke, and that embolic events from occult AF may have been prevented by effective anticoagulation.(12,13) Additionally, since there was a trend towards decreasing bleeding rate as TTR increased, this led to increasing net benefit as TTR increased. Of note, this benefit occurred in a nearly linear fashion without any particular threshold value.

The role of newer oral anticoagulants in preventing adverse events in patients with HF without AF remains undefined. Although WARCEF clearly demonstrated a reduction in ischemic stroke with use of warfarin compared with aspirin, this was counterbalanced by the increase in bleeding episodes.(7) WARCEF did not demonstrate a reduction in death for warfarin group compared to aspirin group. However, since continued warfarin use is not

always adhered to in warfarin treated patients often due to required repeated blood checks, use of non-vitamin K oral anticoagulants which does not require INR checks may improve quality of anticoagulation and thus improve outcomes.(14) Since mortality is reduced as TTR increases, it is possible that the use of newer oral anticoagulants with their more consistent therapeutic anticoagulation effect may reduce deaths. Several clinical trials of newer oral anticoagulants in AF patients analysed their effectiveness in HF.(15–17) These studies showed that the benefit was at least similar (and sometimes better) when compared to warfarin. The stroke rate amongst AF patients with reduced LVEF in ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) Trial was significantly lower compared with warfarin treated patients.(17) Furthermore, since the major bleeding rates are generally lower with newer oral anticoagulants than with warfarin, these agents may deliver a positive net clinical benefit.(18,19)

A major limitation of the current study is that it is not clear from our analysis how factors other than TTR influenced the beneficial effect associated with higher TTR beyond baseline variables. Such factors as geographical location, better care for patients, adherence to HF medical therapy and regularly scheduled test are associated with better TTR, and many of these factors will improve outcomes.(20–23) Additionally, since there was no placebo group, whether patients treated with warfarin would do better than those without either warfarin or aspirin treatment remains unknown. As such, a direct cause-effect relationship between higher TTR and better outcomes is not shown in our current analysis. However, better outcome as TTR increases, and high TTR group having lower event rate compared with the low TTR or the aspirin group, is consistent with a therapeutic effect of anticoagulants.

In conclusion, increasing TTR was associated with better outcomes in the WARCEF trial, with a reduction in death and improved net clinical benefit in HF patients in SR. We suggest that patients with HF in SR in whom good quality anticoagulation can be achieved may benefit from the use of anticoagulants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics and adverse events of patients in the high TTR (final TTR≥60%), low TTR (final TTR<60%), and Aspirin groups. Values are expressed as mean±SD, number/total number (%) or number (KM%), where appropriate.

Covariate	High TTR (n=569)	Low TTR (n=498)	Aspirin (n=1150)	p-value*
Age - yr	62.2± 11.2	59.1± 11.8	60.7± 11.1	<0.001
Location				0.002
AR	17/569 (3.0)	22/498 (4.4)	50/1150 (4.3)	.
EU	296/569 (52.0)	201/498 (40.4)	559/1150 (48.6)	.
NA	256/569 (45.0)	275/498 (55.2)	541/1150 (47.0)	.
Male sex	462/569 (81.2)	384/498 (77.1)	926/1148 (80.7)	0.180
Non-hispanic white	481/569 (84.5)	328/498 (65.9)	866/1147 (75.5)	<0.001
Height - cm	172.0± 8.9	171.2± 9.6	171.7± 9.2	0.402
Weight - kg	86.3± 18.8	85.1± 20.9	86.6± 19.3	0.379
Body-mass index	29.1± 5.6	28.9± 6.4	29.3± 6.0	0.480
Systolic blood pressure - mmHg	123.3± 18.1	124.4± 20.4	124.1± 18.4	0.566
Diastolic blood pressure - mmHg	73.3± 11.2	74.8± 11.9	74.4± 11.3	0.075
Pulse - beats/min	71.1± 11.5	72.8± 11.5	72.0± 12.5	0.069
Hypertension	311/547 (56.9)	309/484 (63.8)	688/1116 (61.6)	0.056
Diabetes Mellitus	183/568 (32.2)	164/497 (33.0)	349/1144 (30.5)	0.556
Atrial Fibrillation	20/568 (3.5)	16/498 (3.2)	42/1144 (3.7)	0.898
Myocardial Infarction	296/568 (52.1)	217/497 (43.7)	558/1144 (48.8)	0.022
Ischemic Cardiomyopathy	260/568 (45.8)	195/497 (39.2)	497/1143 (43.5)	0.093
Peripheral Vascular Disease	63/569 (11.1)	67/498 (13.5)	125/1150 (10.9)	0.298
Prior stroke or TIA	60/568 (10.6)	80/497 (16.1)	137/1145 (12.0)	0.017
Smoking status				<0.001
Current smoker	88/568 (15.5)	118/497 (23.7)	194/1146 (16.9)	.
Former smoker	322/568 (56.7)	216/497 (43.5)	591/1146 (51.6)	.
Never smoked	158/568 (27.8)	163/497 (32.8)	361/1146 (31.5)	.
Alcohol Consumption				0.631

Covariate	High TTR (n=569)	Low TTR (n=498)	Aspirin (n=1150)	p-value*
Current consumption, >2 oz/day	148/569 (26.0)	114/498 (22.9)	289/1146 (25.2)	.
Previous consumption, >2 oz/day	115/569 (20.2)	117/498 (23.5)	253/1146 (22.1)	.
Never consumed alcohol	306/569 (53.8)	267/498 (53.6)	604/1146 (52.7)	.
Educational level				0.300
< High school	248/569 (43.6)	207/498 (41.6)	496/1144 (43.4)	.
High-school graduate or some college	235/569 (41.3)	223/498 (44.8)	455/1144 (39.8)	.
College graduate or postgraduate	86/569 (15.1)	68/498 (13.7)	193/1144 (16.9)	.
NYHA class III or IV	154/567 (27.2)	183/497 (36.8)	340/1141 (29.8)	0.002
Ejection fraction - %	24.8± 7.5	24.4± 7.6	24.8± 7.6	0.563
Distance covered on 6-minute walk - m	363.0±141.5	325.0±140.7	356.9±150.6	<0.001
Medications				
Aspirin or other antiplatelet agent	310/437 (70.9)	268/348 (77.0)	635/866 (73.3)	0.158
Warfarin or other oral anticoagulant	50/569 (8.8)	36/498 (7.2)	89/1150 (7.7)	0.617
ACE inhibitor or ARB	562/568 (98.9)	487/496 (98.2)	1127/1145 (98.4)	0.568
Beta-blocker	518/568 (91.2)	444/496 (89.5)	1025/1146 (89.4)	0.497
Aldosterone blocker	210/357 (58.8)	179/276 (64.9)	401/670 (59.9)	0.256
Nitrate	134/568 (23.6)	126/495 (25.5)	254/1146 (22.2)	0.343
Calcium-channel blocker	45/568 (7.9)	46/496 (9.3)	102/1144 (8.9)	0.705
Diuretic	449/568 (79.0)	415/496 (83.7)	921/1146 (80.4)	0.143
Statin	362/441 (82.1)	287/337 (85.2)	694/840 (82.6)	0.481
Pacemaker or defibrillator	135/568 (23.8)	115/498 (23.1)	249/1144 (21.8)	0.617
BUN - mg/dl	24.2± 12.4	23.3± 12.3	23.7± 13.0	0.529
Creatinine - mg/dL	1.2± 0.3	1.2± 0.3	1.1± 0.3	0.690
eGFR	67.3± 20.4	69.1± 21.3	68.9± 20.4	0.243
Hemoglobin - g/dL	14.0± 1.5	14.0± 1.6	14.1± 1.5	0.231
Hematocrit - %	41.9± 4.1	41.5± 4.9	41.9± 4.3	0.307
Sodium - mEq/L	139.6± 3.2	139.5± 3.3	139.6± 5.2	0.925
White blood cell count - x10^9/L	7.6± 2.0	7.3± 2.1	7.5± 2.0	0.146
Potassium - mEq/L	4.5± 0.5	4.5± 0.5	4.5± 0.5	0.147

Covariate	High TTR (n=569)	Low TTR (n=498)	Aspirin (n=1150)	p-value*
Event				
Primary outcome (death, ischemic stroke, or intracerebral hemorrhage)	128 (30.7%)	146 (37.3%)	312 (38.6%)	0.028
Death	117 (28.3%)	131 (34.9%)	257 (34.2%)	0.071
Ischemic stroke	8 (2.6%)	13 (3.3%)	53 (6.5%)	0.001
Major Hemorrhage (first event)	30 (7.3%)	33 (9.5%)	31 (5.1%)	0.001
Net clinical benefit (primary outcome or first major hemorrhage)	147 (34.8%)	167 (42.2%)	325 (40.1%)	0.017

*P-values were calculated using ANOVA F-test for continuous variables, Chi-square test for categorical variables, and log-rank test for time-to-event outcomes.

Table 2

Hazard ratios (HR) of clinical events for every 10% increase in TTR from Cox models (TTR as a time-dependent covariate).

Event	Unadjusted†		Adjusted†‡	
	HR (95% CI) for 10% TTR increase	p-value	HR (95% CI) for 10% TTR increase	p-value
Primary outcome	0.94(0.90, 0.98)	0.002	0.92(0.89, 0.96)	<0.001
Death	0.94(0.90, 0.98)	0.006	0.93(0.89, 0.97)	0.001
Ischemic stroke	0.88(0.77, 1.02)	0.082	0.88(0.76, 1.02)	0.082
Major Hemorrhage*	0.95(0.87, 1.04)	0.247	0.93(0.85, 1.02)	0.109
Net clinical benefit (primary outcome or major hemorrhage*)	0.93(0.89, 0.96)	<0.001	0.91(0.87, 0.95)	<0.001

*Only the first major hemorrhage for a patient was counted.

†Analyses stratified by Continent.

‡Analyses adjusted for age, body-mass index, diabetes mellitus, ischemic cardiomyopathy, peripheral vascular disease, ejection fraction, 6-minute walk, diuretics and creatinine for primary outcome and death; adjusted for peripheral vascular disease and BUN for ischemic stroke; adjusted for age and 6-minute walk for major hemorrhage; adjusted for age, body-mass index, diabetes mellitus, ischemic cardiomyopathy, peripheral vascular disease, ejection fraction, 6-minute walk, and BUN for net clinical benefit.

Table 3

Comparison of primary outcome by groups from Cox models (with time-dependent high/low TTR group)

	Unadjusted*		Adjusted*†	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
High TTR vs. low TTR	0.76 (0.60, 0.96)	0.021	0.74 (0.58, 0.94)	0.015
High TTR vs. Aspirin	0.81 (0.66, 0.99)	0.044	0.76 (0.62, 0.94)	0.010
Low TTR vs. Aspirin	1.07 (0.88, 1.30)	0.496	1.03 (0.84, 1.25)	0.790

*Analyses stratified by Continent.

†Analyses adjusted for age, body-mass index, diabetes mellitus, ischemic cardiomyopathy, peripheral vascular disease, ejection fraction, 6-minute walk, diuretics and creatinine.