Quality of Anticoagulation Control in Preventing Adverse Events in Patients With Heart Failure in Sinus Rhythm

Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction Trial Substudy

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

Methods and Results—We used data from the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial 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-treated patients, with TTR being treated as a time-dependent covariate. A total of 2217 patients were included in the analyses; among whom 1067 were randomized to warfarin and 1150 were randomized to aspirin. The median (interquartile range) 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 2 outcomes, but significance was not reached (adjusted $P=0.082$ for ischemic stroke and adjusted $P=0.109$ for major hemorrhage).

Conclusions—In patients with heart failure in sinus rhythm, 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.

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Key Words: anticoagulant ■ heart failure ■ hemorrhage ■ stroke

Anticoagulation with warfarin is widely used to prevent stroke and other thromboembolic events. Efficacy and safety of vitamin K antagonists, such as warfarin, are dependent on the quality of anticoagulation control as reflected by the average time each patient spends in the 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,

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A full list of WARCEF Investigators is available in the Data Supplement.

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the effect 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 versus 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 end point of stroke (ischemic and hemorrhagic) or death combined did not differ between the 2 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. In addition, we explored the major hemorrhage rate in relation to TTR in patients with HF. As far as we are aware, this is the first study to assess warfarin effectiveness and bleeding rate classified by TTR in patients with HF in SR.

Methods

Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction Trial

This analysis used information obtained from the double-blind WARCEF trial (http://www.ClinicalTrials.gov; number, NCT00041938), in which patients with left ventricular EF ≤35% in SR were randomly assigned to warfarin (target international normalized ratio [INR)], 2.75; with an acceptable INR range of 2.0–3.5) or aspirin (325 mg per day). The design has been previously reported.[7] The primary efficacy outcome was the 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 >2 g hemoglobin decline in 48 hours, those requiring 2 units or more of transfusion, or requiring hospitalization or surgical intervention. This 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 INRs were imputed. We assumed that any change between 2 consecutive INR measurements takes place linearly for a 5-day period. For the time period between 2 consecutive INR measurements, we imputed INR backward 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 2 INR values.[8] A 6-week 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 seventh week for which the patient was in the TTR (INR of 2–3.5). The final TTR for each patient is the patient's TTR at the end of follow-up. Seventy-five warfarin-treated patients either had a follow-up time of <6 weeks or were on interruption of therapy after 6 weeks, and thus missing TTR throughout the study. These patients were excluded from the analyses. To allow for a fair comparison, 13 aspirin-treated patients with a follow-up time of <6 weeks were also excluded, giving a total sample of 2217 patients.

We divided warfarin-treated patients into 2 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 2 groups and aspirin-treated patients using an ANOVA F-test for continuous variables, χ^2 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 effect 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 the 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, that is, 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 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% confidence interval 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 2217 patients, 1067 were randomized to warfarin and 1150 patients to aspirin. Overall median (interquartile range) follow-up was 3.6 (2.0–5.0) years. Descriptive statistics for patient variables and adverse events are shown in Table 1. Overall, 71461 INRs were analyzed in 5 laboratories that represented geographic locations of the study sites (North America, South America, and 3 locations in Europe). The mean (±SD) final TTR per patient was 57% (±28.5%) for warfarin-treated patients, lower than the overall proportion of TTR reported in the primary WARCEF article because patients with shorter times on warfarin had lower TTRs.[7] When patients were not in the TTR, on average, more time was spent below the TTR (32.4±28.9%) than above (10.5±12.9%).

Results showing the effect of time-dependent TTR on time-to-event outcomes are presented in Table 2. In 3 of the 5 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 the 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-treated 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-treated group (aHR=0.76; P=0.010), whereas 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 patients with HF in SR, increasing TTR is associated with better outcomes

Table 1. Characteristics and Adverse Events of Patients in the High TTR (Final TTR≥60%), Low TTR (final TTR<60%), and Aspirin-Treated Groups

Covariates	High TTR, n=569	Low TTR, n=498	Aspirin, n=1150	*P* Value*
Age, y	62.2±11.2	59.1±11.8	60.7±11.1	<0.001
Location				
AR	17/569 (3.0)	22/498 (4.4)	50/1150 (4.3)	0.002
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, mm Hg	123.3±18.1	124.4±20.4	124.1±18.4	0.566
Diastolic blood pressure, mm Hg	73.3±11.2	74.8±11.9	74.4±11.3	0.075
Pulse, beats per minute	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
Previous stroke or TIA	60/568 (10.6)	80/497 (16.1)	137/1145 (12.0)	0.017
Smoking status				
Current smoker	88/568 (15.5)	118/497 (23.7)	194/1146 (16.9)	<0.001
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				
Current consumption, >2 oz/d	148/569 (26.0)	114/498 (22.9)	289/1146 (25.2)	0.631
Previous consumption, >2 oz/d	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				
<High school	248/569 (43.6)	207/498 (41.6)	496/1144 (43.4)	0.300
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
β-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

(*Continued*)

Table 1. Continued

Covariates	High TTR, n=569	Low TTR, n=498	Aspirin, n=1150	*P* Value*
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, $\times 10^9$ per 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
Events				
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

Values are expressed as mean±SD, number/total number (%), or number (KM%), where appropriate. ACE indicates angiotensin-converting enzyme; AR, Argentina; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; eGFR, epidermal growth factor receptor; EU, Europe; KM, Kaplan-Meier; NA, North America; NYHA, New York Heart Association; TIA, transient ischemic attack; and TTR, therapeutic range.

*P values were calculated using ANOVA F-test for continuous variables, χ^2 test for categorical variables, and log-rank test for time-to-event outcomes.

and improved net clinical benefit. Patients with high TTR fared better than patients with low TTR and those receiving aspirin. On the other hand, patients with low TTR tended to do similarly compared with 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 were observed for primary event, death alone, and for net clinical benefit. There was a trend toward better stroke outcomes with high TTR, but this did not reach statistical significance. Patients with high TTR 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 because of microembolization.[10] It is possible that such events were prevented in our study by the use of warfarin, thus

Table 2. HRs of Clinical Events for Every 10% Increase in TTR From Cox Models (TTR as a Time-Dependent Covariate)

	Unadjusted†		Adjusted†‡	
Event	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

BUN indicates blood urea nitrogen; CI, confidence interval; HR, hazard ratio; and TTR, therapeutic range.

*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

CI indicates confidence interval; HR, hazard ratio; and TTR, therapeutic range.

*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.

leading to lower rate of death. It is also known that patients with HF tend to develop AF.[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] In addition, because there was a trend toward 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-treated group compared with aspirin-treated group. However, because continued warfarin use is not always adhered to in warfarin-treated patients often because of 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] Because 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 patients with AF analyzed their effectiveness in HF.[15–17] These studies showed that the benefit was at least similar (and sometimes better) when compared with warfarin. The stroke rate among AF patients with reduced left ventricular EF in Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial was significantly lower compared with warfarin-treated patients.[17] Furthermore, because 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 this 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] In addition, because 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-treated 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 patients with HF 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.

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CLINICAL PERSPECTIVE

We assessed whether time in the therapeutic range is associated with clinical outcomes in heart failure patients in sinus rhythm treated with warfarin. In 1067 patients randomized to warfarin in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, higher time in the therapeutic range was significantly associated with decreased risk of primary outcome, defined as ischemic stroke, intracerebral hemorrhage, or death (adjusted hazard ratio for each 10% increase in time in the therapeutic range of 0.92, 95% confidence interval of 0.89–0.96, and $P<0.001$). Similarly, higher therapeutic range was significantly associated with decreased risk of death alone, as well as with net clinical benefit defined as the primary outcome or major hemorrhage. Our findings suggest that in patients with heart failure who are in sinus rhythm, those in whom good quality anticoagulation can be achieved may benefit from the use of anticoagulants.

Quality of Anticoagulation Control in Preventing Adverse Events in Patients With Heart Failure in Sinus Rhythm: Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction Trial Substudy

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동리듬의 구혈률저하 심부전 환자에서도 항응고요법이 적절하면 예후가 개선될 수 있다 : WARCEF Trial Substudy

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초록

배경

본 연구의 목적은 동리듬의 심부전 환자를 와파린으로 치료할 때 목표 치료범위(time in the therapeutic range, TTR)와 향후 임상사건의 발생이 서로 연관이 있는지를 알아보고자 함이다.

방법 및 결과

Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction(WARCEF) 연구의 하위 분석으로, TTR과 다음의 임상사건과의 연관성을 평가하였다; WARCEF 연구의 일차 종료점(허혈성 뇌졸중, 뇌출혈, 혹은 사망의 합), 사망, 뇌졸중, 주요 출혈, 전체 임상 효과(일차 종료점과 주요 출혈의 합). TTR에 따른 사건 위험의 변화를 확인하고, 고-TTR군, 저-TTR군, 아스피린 치료군을 비교하기 위해 다변량 Cox 모델이 사용되었다. 전체 2,217명의 환자는 와파린 치료군 1,067명, 아스피린 치료군 1,150명으로 무작위 배정되었다. 추적 기간의 중앙값은 3.6(2.0-5.0)년이었고, 대상 환자의 평균 연령은 61±11.3세이며, 남성이 80%였다. 그리고 평균 TTR은 57±28.5%였다. 고-TTR군은 일차 종료점(adjusted P<0.001)과 사망(adjusted P=0.001)이 유의하게 낮았고, 전체 임상 효과는 개선되었다(adjusted P<0.001). 다른 두 임상사건의 결과도 비슷한 양상을 보이긴 했으나, 임상적 유의성은 없었다(허혈성 뇌졸중, adjusted P=0.082; 주요 출혈, adjusted P=0.109).

결론

동리듬의 심부전 환자에서 와파린을 투여하면서 TTR이 잘 유지될 경우, 향후 임상사건의 발생이 감소하고 전체 임상 효과는 개선된다. 따라서, 양질의 항응고요법은 동리듬의 심부전 환자에서 효과적일 수 있다.