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Heart Failure Severity and Quality of Warfarin Anticoagulation Control (From the WARCEF Trial)

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Abstract

Previous studies among patients with atrial fibrillation showed that a history of heart failure (HF) could negatively impact anticoagulation quality, as measured by the average time in therapeutic

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The investigators in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Study Group are listed in the Supplementary Appendix

Conflict of interest

Dr. Anker reports consultancy for Janssen (minor) - steering committee for COMMANDER-HF. Dr. Homma reports being a consultant for St. Jude Medical, Daiichi-Sankyo, Bristol Meyers Squibb, Pfizer. Dr. Labovitz has received a research grant from Bristol-Myers Squibb/Pfizer for the AREST trial. Dr. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola, and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis. Dr. Sacco has received research grants from NINDS, NCATS, AHA, Evelyn McKnight Brain Foundation and Boehringer Ingelheim. Dr. Teerlink has received consulting fees/research grants from Actelion, Amgen, Bayer, Cytokinetics, Medtronic, Novartis, St. Jude, Trevena. The other authors have no relationships to report.

range (TTR). Whether additional markers of HF severity are associated with TTR has not been investigated thoroughly. We aimed to examine the potential role of HF severity in the quality of warfarin control among patients with HF with reduced ejection fraction. Data from the Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction Trial (WARCEF) were used to investigate the association between TTR and HF severity. Multivariable logistic regression models were used to examine the association of markers of HF severity, including New York Heart Association (NYHA) class, Minnesota Living with Heart Failure (MLWHF) score and frequency of HF hospitalization, with TTR ≥ 70% (high TTR). We included 1 067 participants (high TTR, N=413; low TTR, N=654) in the analysis. In unadjusted analysis, patients with a high TTR were older and less likely to have had strokes or receive other antiplatelet agents. Those patients also had lower NYHA class, better MLWHF scores, greater 6-minute walk distance and lower frequency of HF hospitalizations. Multivariable analysis showed that NYHA class III/IV (OR:0.68 [95% confidence intervals:0.49 to 0.94]), each 10-point increase in MLWHF score (i.e. worse health-related quality of life) (OR: 0.92 [0.86 to 0.99]), and higher number of HF hospitalization per year (OR:0.45 [0.30 to 0.67]) were associated with decreased likelihood of having high TTR. In HF patients with systolic dysfunction, NYHA class III/IV, poor health-related quality of life and a higher rate of HF hospitalization were independently associated with suboptimal quality of warfarin anticoagulation control. These results affirm the need to assess the new approaches, such as direct oral anticoagulants, to prevent thromboembolism in this patient population.

Keywords

Heart Failure; Quality and Outcomes; Thrombosis; Warfarin

Both American[1,2] and European[3] guidelines for the management of heart failure (HF) recommend anticoagulation for select HF patients, such as those with atrial fibrillation (AF) to prevent thromboembolism. In this setting, warfarin remains a common choice for anticoagulation, necessitating periodic monitoring of the international normalized ratio (INR) to adjust dosage. In patients on warfarin, high quality of anticoagulation, as measured by the average time in therapeutic range (TTR), is associated with less thromboembolic event such as stroke or myocardial infarction.[4,5] Previously using the data of patients with HF with reduced ejection fraction (HFrEF) and sinus rhythm from the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial[6], we have demonstrated that patients on warfarin with high TTR is associated with improved net clinical benefit compared both with patients on warfarin with low TTR and patients on aspirin only.[7] Unlike patients with AF, however, knowledge who tend to have a better anticoagulation among HFrEF patients is limited despite of high incidence of thrombosis among this population. We therefore undertook the present analysis of HFrEF patients enrolled in the WARCEF trial[6] to investigate the association between HF severity and TTR.

METHODS

The protocol of the randomized, double-blinded WARCEF trial (http://www.ClinicalTrials.gov Trial Reg no. NCT00041938) has been described previously.[6] Briefly, participants with LVEF ≤ 35% who were in sinus rhythm were randomized to

receive warfarin or aspirin. Additional eligibility criteria included age ≥ 18 years old, having no contraindications to warfarin, having a modified Rankin score of ≤ 4, and on evidence-based heart failure medications (beta-blocker, angiotensin-converting enzyme [ACE] inhibitor, or angiotensin II receptor blockers [ARB], or hydralazine and nitrates). Participants were excluded if they had a clear indication for warfarin or aspirin, or if they had a condition that conferred a high risk of cardiac embolism. A total of 2,305 participants (warfarin arm, N=1,142; aspirin arm, N=1,163) were randomized from 168 centers in 11 countries from October 2002 to January 2010. The mean follow-up time was 3.5 ± 1.8 years. Institutional Review Boards at the coordinating centers for all sites approved the study, and all participants provided informed consent.

For this analysis, we included participants from the warfarin arm of the WARCEF trial only. Of these, 75 were excluded because they either had follow-up time less than six weeks or had a continuous interruption of warfarin therapy after six weeks and therefore had missing TTR throughout the study. The final study sample thus included 1,067 participants.

Assessment of TTR in WARCEF participants was described previously[6,7]. Briefly, 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 until five days after the first measurement. Then we imputed the first five days using linear interpolation of these two INR values.[8] As an example, if the measured INR was 1.0 on day 1 and 2.0 on day 10, the imputed INRs are 1.2, 1.4, 1.6, and 1.8 on day 2, 3, 4, and 5, respectively, and are 2.0 on days 6 to 9. A six-weeks initial titration phase is allowed. The TTR for each patient is the patient's percentage of time on warfarin for which the patient was in therapeutic range (INR of 2 to 3.5) from the 7th week to the end of follow-up. Based on the previous literature[9], final TTR ≥ 70% were defined as the high TTR group and the rest as the low TTR group.

For this analysis, we considered the rate of HF hospitalizations per year as a marker of HF severity. An independent end-point adjudication committee adjudicated all outcomes and major adverse events in WARCEF, and HF hospitalizations were defined as hospital admission for HF or hospitalization for which HF was a major contributing factor for admission and which met all of the following criteria:1) signs and symptoms of HF on admission; 2) admission to the hospital for at least 24 hours, excluding time in an emergency room or observation unit; and 3) the use of intravenous diuretic, vasodilator, or inotropic therapy for the purposes of treating HF. We also considered New York Heart Association (NYHA) functional class as a measure of severity of HF symptoms and exercise capacity, as well as health-related quality of life measured by the Minnesota Living With Heart Failure (MLWHF) questionnaire, which has been shown to be a powerful predictor of morbidity and mortality among HF patients.[10] MLWHF score was categorized in three groups (MLWHF score: 0–23, good; 24–45, moderate; 45–105, poor quality of life)[11]. Finally, we measured exercise capacity of the participants quantitatively by the distance walked in six minutes.

To address all possible associations between clinical variables and high TTR, we considered all baseline characteristics obtained in the trial (Table 1). Briefly, for independent variables, we included demographic characteristics such as age, sex, race/ethnicity, education, and

clinical characteristics including vitals (height, weight, body mass index, systolic and diastolic blood pressure, pulse rate), life style risk factors (smoking status, alcohol consumption), comorbidities and past medical history, medications, laboratory data, and LV ejection fraction. The definitions of each variable were detailed elsewhere[6].

Data analysis was conducted SAS software version 9.4 [SAS Institute Inc., Cary, NC]. Participants' characteristics are presented as the mean ± standard deviation (SD) for continuous variables and as a proportion for categorical variables. These values were compared between high TTR group and low TTR group using a two-sample *t*-test for continuous variables and χ^2 test for categorical variables. Logistic regression models were used to assess the association between the high TTR and clinical/demographic variables. We also used restricted cubic splines in univariable models to check the potential nonlinear association between high TTR and each variable. In all models, the outcome was high TTR. The final multivariable model was built using forward-backward stepwise selection with entry and removal criteria of $p = 0.05$. Missing values of baseline variables were imputed using means for continuous variables and modal values for categorical variables. For all statistical analyses, a two-tailed $P < 0.05$ was considered significant.

RESULTS

For the 1,067 WARCEF participants on warfarin therapy included in this analysis, the mean TTR was 62.6%. INR values were below 2.0 for 27.1% of the total treatment time and above 3.5 for 10.3% of the total treatment time. The mean INR value during treatment was 2.5 ± 0.95.

Table 1 presents the descriptive data categorized by TTR ≥ 70% or not. The participants with high TTR were older, more likely to have a history of myocardial infarction, worse kidney function, higher pulse, better MLWHF score, longer distance walked in 6 minutes, and fewer HF hospitalization. These participants were less likely to have hypertension, history of stroke or transient ischemic attack, and to be on other antiplatelet agents.

Relations between HF severity and TTR are depicted in Figure 1. Those with higher rate of HF hospitalization were likely to have low TTR: the median TTR of 0, 0–1, and >1 HF hospitalization per year was 64.9, interquartile range (IQR) [42.7–80.3], 58.0 [31.0–73.3], and 35.2 [8.1–58.8], $p < 0.001$, respectively (Figure 1A). For NYHA class, the median TTR among participants with NYHA I/II and III/IV were 65.8, IQR [42.7–80.3] and 56.4 [33.1–73.7], $p < 0.001$, respectively (Figure 1B). Higher health-related quality of life was associated with higher TTR: the median TTR of good, moderate, poor quality of life was 68.8, IQR [48.7–82.7], 63.3 [44.5–77.4], and 52.0 [21.1–73.9], $p < 0.001$, respectively (Figure 1C).

In the multivariable model after the stepwise selection, we found a higher number of HF hospitalization per year, NYHA class III/IV, and each 10-point increase in MLWHF score were independently associated with decreased likelihood of having high TTR ≥ 70%. Other significant predictors of high TTR were location, older age, race/ethnicity, greater weight, smoking status and other antiplatelet medications (as detailed in Table 2).

DISCUSSION

The present study demonstrated for the first time that markers of HF severity are associated with TTR. In our analysis of patients with HFrEF and sinus rhythm enrolled in WARCEF, HF severity were associated with the quality of anticoagulation independent of other important clinical factors. Our results suggest that for patients with HF being considered for warfarin therapy, those with more advanced HF may have more difficulty in achieving high quality of anticoagulation.

Although warfarin titration in HF patients is known to be challenging[12,13], there are several potential mechanisms for why HF severity may be an important risk factor for suboptimal TTR. It is possible that patients with more severe HF may have poorer adherence to taking warfarin or to follow-ups for INR.[14] It is also possible that fluctuating volume status with intermittent volume overload from HF can affect intestinal absorption[15] and metabolism of warfarin. For example, HF induced malabsorption of vitamin K or insufficient intake of vitamin K may predispose patients taking warfarin to INR elevations.[16] Likewise, liver impairment due to congestive HF[17] may interact warfarin response because the hepatic enzyme is responsible for oxidative metabolism of warfarin[18], while also leading to insufficient production of clotting factors and platelets. There may also be an interaction between cardiovascular comorbidities and genetic determinants of warfarin metabolism, such as CYP2C9 and VKORC1 mutations.[19–21] Further research is needed to clarify these mechanisms.

Previous studies have examined the factors affecting quality of warfarin anticoagulation in patients with AF[22–26] and identified that the patients with HF were less likely to achieve target INR range.[22,24] For instance, the SAMe-TT_2R_2[22] score was developed from the cohort of the AFFIRM (AF Follow-up Investigation of Rhythm Management) trial and externally validated in prospectively recruited 286 patients. They identified following factors were associated with suboptimal warfarin anticoagulation: female, less than 60 years of age, history of comorbidities such as hypertension, diabetes, coronary artery disease, peripheral arterial disease, congestive HF, stroke, pulmonary disease, liver or renal disease, medications which have interaction with warfarin such as amiodarone, tobacco use within 2 years and non-white race. Although mixed results have been observed in other studies[22–26], younger age, female, and non-white race/ethnicity were consistently associated with unfavorable INR control. Our findings are broadly similar. In our analysis, we confirmed that younger age and non-Hispanic black race/ethnicity were associated with low TTR. Although the specific mechanism of association between older age and warfarin control is unknown, a possible explanation is that older patients tend to have higher medication adherence than younger patients.[27] In contrast to previous studies, female sex was not independently associated with quality of anticoagulation control in our analysis, possibly due to the modest number of female participants in the WARCEF trial (approximately 20%).

For specific HF patients, such as those with AF or with a high risk for cardioembolism, both American and European current guidelines recommend anticoagulation to prevent thromboembolism.[1–3] Although not directly addressed by our analysis, we suspect that predictors of suboptimal TTR would be similar to patients with HFrEF who have other

indications for anticoagulation. Identifying such patients may be useful to determine the optimal target population for the use of direct oral anticoagulants (DOACs) as DOACs have favorable risk-benefit profiles.[28] Given that optimal warfarin anticoagulation may be difficult to achieve especially in patients with more severe HF, our results also affirms the need to assess the effect of DOACs in this population, such as through the ongoing COMMANDER HF trial, which seeks to assess the effectiveness and safety of rivaroxaban in reducing the risk of death, myocardial infarction or stroke in participants with HF and coronary artery disease following an episode of decompensated HF (https://ClinicalTrials.gov/show/NCT01877915).

There are several limitations to address. First, the cross-sectional design of our study limits causal inference for the relationship between the quality of anticoagulation and HF severity. Second, we could not exclude the possibility that a hereditary predisposition contributed to warfarin resistance because we did not collect the information about genetic polymorphisms. However, the previous randomized trial has shown that baseline genetic testing on sensitivity to warfarin does not affect clinically important outcomes[29]. Third, the generalizability of our study might be limited because the WARCEF population included only HFrEF patients in sinus rhythm. While we expect similar mechanisms to be at play for HF patients in general, generalizability to HFrEF patients with AF will need to be validated in future studies. Fourth, the standard of care for HF during the WARCEF trial may differ from contemporary practice. It is reassuring that background pharmacological therapy for WARCEF participants are largely similar to the current era though angiotensin receptor-neprilysin inhibitor was not yet available as a treatment option, with >98%, 90%, 60% of patients receiving an ACE inhibitor or ARB, a beta-blocker, or a mineralocorticoid receptor antagonist, respectively. However, potential confounding may remain from unmeasured differences in how heart failure or anticoagulation were managed during the WARCEF era compared to the current one. Fifth, we did not measure the severity of HF by using existing risk scores such the MAGGIC Risk Score[30], as we did not capture the data elements necessary to calculate such scores.

In conclusion, a higher rate of HF hospitalizations, NYHA class III/IV, and poor quality of life were independently associated with suboptimal warfarin anticoagulation control among HF patients with reduced ejection fraction. These results affirm the need to assess the new approaches, such as direct oral anticoagulants, to prevent thromboembolism in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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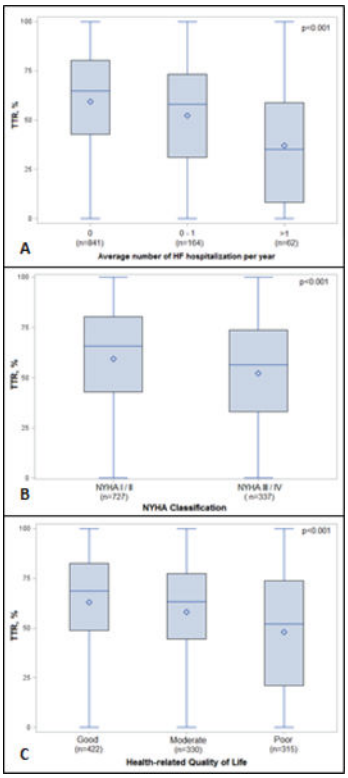

Figure 1.

Heart Failure severity and quality of warfarin anticoagulation

A. Average number of HF hospitalization per year B. NYHA class C. Health-related quality of life

HF, heart failure; TTR, time in therapeutic range; NYHA, New York Heart Association; MLWHF score, Minnesota Living with Heart Failure score.

Quality of warfarin anticoagulation was measured by measured by the average time in therapeutic range (TTR). Health-related quality of life was measured by Minnesota Living with Heart Failure (MLWHF) score. MLWHF score was categorized in three groups (MLWHF score: 0–23, good; 24–45, moderate; 45–105, poor health-related quality of life).

Table 1

Participants characteristics by time in therapeutic range

Variables	Time in therapeutic range ≥ 70% (n=413)	Time in therapeutic range < 70% (n=654)	p-value
Location			<0.001
Argentina	16/413 (3.9%)	23/654 (3.5%)	.
Europe	226/413 (54.7%)	271/654 (41.4%)	.
North America	171/413 (41.4%)	360/654 (55.0%)	.
Age (years)	62.8±11.1	59.4±11.7	<0.001
Men	337/413 (81.6%)	509/654 (77.8%)	0.139
Non-Hispanic white	356/413 (86.2%)	453/654 (69.3%)	<0.001
Non-Hispanic black	21/413 (5.1%)	128/654 (19.6%)	.
Hispanic	27/413 (6.5%)	54/654 (8.3%)	.
Other	9/413 (2.2%)	19/654 (2.9%)	.
Educational level			0.281
< High school	187/413 (45.3%)	268/654 (41.0%)	.
High school +	165/413 (40.0%)	293/654 (44.8%)	.
College +	61/413 (14.8%)	93/654 (14.2%)	.
Height (cm)	172.0±9.0	171.3±9.4	0.254
Weight (kg)	86.1±19.0	85.5±20.3	0.658
Systolic blood pressure (mmHg)	123.2±17.9	124.2±20.0	0.398
Diastolic blood pressure (mmHg)	73.3±11.3	74.4±11.7	0.133
Pulse (beats/min)	70.6±11.2	72.7±11.6	0.003
Body-mass index (kg/m^2)	29.0±5.5	29.0±6.3	0.891
Smoking status			0.001
Current	59/412 (14.3%)	147/653 (22.5%)	.
Former	234/412 (56.8%)	304/653 (46.6%)	.
Never	119/412 (28.9%)	202/653 (30.9%)	.
Alcohol Consumption (oz/day)			0.110
Current, >2	106/413 (25.7%)	156/654 (23.9%)	.
Previous, >2	76/413 (18.4%)	156/654 (23.9%)	.
Never	231/413 (55.9%)	342/654 (52.3%)	.
Hypertension	215/397 (54.2%)	405/634 (63.9%)	0.002
Prior stroke or TIA	42/412 (10.2%)	98/653 (15.0%)	0.024
Atrial Fibrillation	15/412 (3.6%)	21/654 (3.2%)	0.705
Myocardial Infarction	222/412 (53.9%)	291/653 (44.6%)	0.003
Diabetes Mellitus	131/412 (31.8%)	216/653 (33.1%)	0.664
Ischemic Cardiomyopathy	193/412 (46.8%)	262/653 (40.1%)	0.031
Peripheral Vascular Disease	47/413 (11.4%)	83/654 (12.7%)	0.524
Living with ICD	73/412 (17.7%)	119/654 (18.2%)	0.843
Hematocrit (%)	41.9±4.1	41.6±4.7	0.330
eGFR ($mL/min/1.73\ m^2$)	66.3±19.9	69.3±21.3	0.018

Variables	Time in therapeutic range ≥ 70% (n=413)	Time in therapeutic range < 70% (n=654)	p-value
Left ventricular ejection fraction (%)	24.8±7.2	24.5±7.7	0.525
NYHA class			0.002
I	64/411 (15.6%)	76/653 (11.6%)	.
II	245/411 (59.6%)	342/653 (52.4%)	.
III	98/411 (23.8%)	224/653 (34.3%)	.
IV	4/411 (1.0%)	11/653 (1.7%)	.
Baseline MLWHF score	29.0±21.2	37.7±24.8	<0.001
Distance covered on 6-minute walk (meters)	362.9±145.2	334.2±139.4	0.002
Average number of HF hospitalization per year	0.2±0.7	0.6±1.4	<0.001
Aspirin	220/388 (56.7%)	353/596 (59.2%)	0.432
Other antiplatelet agent	6/173 (3.5%)	23/228 (10.1%)	0.011
ACE Inhibitor	344/412 (83.5%)	556/652 (85.3%)	0.433
ARB	72/412 (17.5%)	100/652 (15.3%)	0.356
Beta-blocker	374/412 (90.8%)	588/652 (90.2%)	0.749
Calcium-channel blocker	33/412 (8.0%)	58/652 (8.9%)	0.615
Diuretic	322/412 (78.2%)	542/652 (83.1%)	0.043
Statin	264/322 (82.0%)	385/456 (84.4%)	0.367
Aldosterone blocker	148/252 (58.7%)	241/381 (63.3%)	0.252

TIA, temporary ischemic attack; ICD, implantable cardioverter–defibrillator; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; NYHA, New York Heart Association; MLWHF, Minnesota Living With Heart Failure; HF, heart failure.

Table 2

Association between time in therapeutic range ≥ 70 % and clinical factors

		Univariable model		Multivariable model	
Variables	**For a change of**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Location					
Argentina		reference	< 0.001	reference	0.007
Europe		1.2 (0.62,2.32)		0.82 (0.30,2.25)	
North America		0.68 (0.35,1.33)		0.52 (0.20,1.37)	
Age (years)	10	1.30 (1.16,1.45)	< 0.001	1.28 (1.12, 1.46)	< 0.001
Men		1.26 (0.93,1.72)	0.139		
Non-Hispanic white		reference	< 0.001	reference	< 0.001
Hispanic		0.64 (0.39,1.03)		0.6 (0.29,1.25)	
Non-Hispanic black		0.21 (0.13,0.34)		0.3 (0.18,0.51)	
Other		0.6 (0.27,1.35)		0.6 (0.26,1.40)	
Educational level					
< High school		reference	0.282	reference	
High school +		0.81 (0.62,1.05)			
College +		0.94 (0.65,1.37)			
Height (cm)		1.01 (0.99,1.02)	0.254		
Weight (kg, Linear Spline)					
< 72.7		1.43 (1.08,1.89)	0.041		
> 72.7		0.95 (0.88,1.03)			
Weight (kg)	10	1.01 (0.95,1.08)	0.657	1.12 (1.04,1.21)	0.004
Systolic BP (mmHg)	10	0.97 (0.91,1.03)	0.397	0.91 (0.85, 0.98)	0.015
Diastolic BP (mmHg)	10	0.92 (0.83,1.03)	0.133		
Pulse (beats/minutes)		0.98 (0.97,0.99)	0.003		
Body-mass index (kg/m^2, Linear Spline)					
< 25.1		1.15 (1.04,1.27)	0.019		
> 25.1		0.98 (0.95,1.00)	.		
Body-mass index (kg/m^2)		1.00 (0.98,1.02)	0.892		
Smoking status					

Variables	For a change of	Univariable model		Multivariable model	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Never		reference	0.001	reference	0.013
Current		0.68 (0.47,0.99)		0.77 (0.51,1.16)	
Former		1.31 (0.99,1.74)		1.32 (0.97,1.79)	
Alcohol consumption (oz/day)					
Never		reference	0.111		
Current, >2		1.01 (0.75,1.36)			
Previous, >2		0.72 (0.52,0.99)			
Hypertension		0.68 (0.53,0.88)	0.003		
Prior stroke or TIA		0.64 (0.44,0.94)	0.024		
Atrial Fibrillation		1.14 (0.58,2.23)	0.711		
Myocardial Infarction		1.45 (1.13,1.86)	0.003		
Diabetes Mellitus		0.94 (0.72,1.23)	0.657		
Ischemic Cardiomyopathy		1.31 (1.02,1.68)	0.032		
Peripheral Vascular Disease		0.88 (0.60,1.29)	0.524		
Living with ICD		0.97 (0.70,1.33)	0.829		
Hematocrit (%, Linear Spline)					
< 39.2		1.12 (1.03,1.21)	0.030		
> 39.2		0.97 (0.93,1.02)			
Hematocrit (%)		1.01 (0.99,1.04)	0.328		
eGFR (mL/min/1.73 m^2)		0.99 (0.99,1.00)	0.019		
LV ejection fraction (%)		1.01 (0.99,1.02)	0.525		
NYHA class III or IV		0.58 (0.44,0.77)	< 0.001	0.68 (0.49,0.94)	0.020
Baseline MLWHF score (points)	10	0.85 (0.80,0.90)	< 0.001	0.92 (0.86, 0.99)	0.017
Distance covered on 6-minute walk (meters)	30	1.04 (1.02,1.07)	0.002		
Average number of HF hospitalizationper year		0.72 (0.61,0.84)	< 0.001	0.45 (0.30,0.67)	< 0.001
Aspirin		0.86 (0.67,1.11)	0.250		
Other antiplatelet agent		0.4 (0.16,1.00)	0.050	0.33 (0.13,0.87)	0.025
ACE Inhibitor		0.87 (0.62,1.22)	0.431		
ARB		1.17 (0.84,1.63)	0.354		
Beta-blocker		1.07 (0.70,1.63)	0.752		

		Univariable model		Multivariable model	
Variables	**For a change of**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Calcium-channel blocker		0.89 (0.57,1.39)	0.617		
Diuretic		0.73 (0.53,0.99)	0.043		
Statin		0.75 (0.51,1.08)	0.121		
Aldosterone blocker		0.81 (0.61,1.08)	0.153		

OR, odds ratio; CI, confidence interval; TIA, temporary ischemic attack; ICD, implantable cardioverter– defibrillator; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; LV, left ventricular; BP, blood pressure; NYHA, New York Heart Association; MLWHF, Minnesota Living With Heart Failure; HF, heart failure.

The final multivariable model was built using forward-backward stepwise selection with entry and removal criteria of p=0.05.