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Aspirin Does Not Increase Heart Failure Events in Heart Failure Patients—from the WARCEF Trial

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Abstract

Objectives—The aim of this study was to determine, in patients with heart failure with reduced ejection fraction (HFrEF) receiving an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), whether aspirin increases heart failure (HF) hospitalization or death.

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Disclosures

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Background—Because of its cyclooxygenase inhibiting properties, aspirin has been postulated to increase HF events in patients treated with ACE inhibitors or ARBs. However, no large randomized trial has addressed the clinical relevance of this issue.

Methods—We compared aspirin and warfarin for HF events (hospitalization, death, or both) in the 2,305 patients enrolled in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial (98.6% on ACE inhibitor or ARB treatment), using conventional Cox models for time to first event (489 events). In addition, to examine multiple HF hospitalizations, we used two extended Cox models, a conditional model and a total time marginal model, in time to recurrent event analyses (1078 events).

Results—After adjustment for baseline covariates, aspirin and warfarin treated patients did not differ in time to first HF event (adjusted HR 0.87; 95% CI 0.72–1.04, p=0.117) or first hospitalization alone (adjusted HR 0.88; 95% CI 0.73–1.06, p=0.168). The extended Cox models also found no significant differences in all HF events, or in HF hospitalizations alone, after adjustment for covariates.

Conclusion—Among patients with HFrEF in the WARCEF trial, there was no significant difference in risk of HF events between the aspirin and warfarin-treated patients.

Clinical Trial Registration—ClinicalTrials.gov number NCT00041938

Keywords

heart failure; aspirin; warfarin; survival; hospitalization

Recommendations for antithrombotic therapy in patients with heart failure (HF) in sinus rhythm (SR) have fluctuated widely over recent decades with varying roles for aspirin and warfarin. On the basis of recent clinical trials (1–3), two major official guidelines have concluded that in patients with chronic HF without atrial fibrillation (AF), a prior thromboembolic event, or a cardioembolic source, there is no evidence that an oral anticoagulant reduces mortality or morbidity compared with placebo or aspirin (4,5). The emergence of novel oral anticoagulants has rekindled interest in the prospect of improving outcomes in HF through an antithrombotic strategy (6–8).

The answer to another major question has remained elusive; in patients treated with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), does aspirin increase HF-related events in patients with heart failure with reduced ejection fraction (HFrEF) compared to those not receiving these medications? This question evolved from recognition that the cyclooxygenase inhibiting properties of aspirin, which reduce prostaglandins and nitric oxide, could be detrimental in HF by counteracting the beneficial effects of ACE inhibitors which increase prostaglandins through inhibition of their degradation (9). Multiple small studies provide some support for this perspective (9,10). In the Warfarin and Antiplatelet Therapy in Chronic Heart failure (WATCH) trial, there was a significant increase in HF hospitalizations in patients treated with aspirin compared to warfarin (2). Given the high incidence of coronary artery disease and coronary artery stenting in the HF population (11,12), the potential adverse impact of aspirin on HF hospitalizations continues to be relevant to the daily care of these patients (13).

We previously reported the results of the Warfarin Aspirin Reduced Cardiac Ejection Fraction trial (WARCEF) in 2,305 patients enrolled and followed for up to six years (1). The result showed that warfarin had significant benefit compared with aspirin with respect to the prevention of ischemic stroke throughout the follow-up period among patients with HFrEF. However, the increase in the incidence of major bleeding offset the benefit of warfarin. Although warfarin reduced ischemic stroke, we found no difference between warfarin and aspirin treated groups with regard to all cause death or stroke (time to first event) and the composite secondary endpoint of death, ischemic stroke, intracranial hemorrhage, myocardial infarction or HF hospitalization (time to first event). We also reported, in an unadjusted secondary analysis, no increase in time to first hospitalization for aspirin compared to warfarin, but did not focus in depth on the effect of aspirin compared to warfarin specifically on HF-related events (1). Furthermore, no large randomized trial has addressed this clinically relevant issue. The purpose of these analyses was to investigate the effect of aspirin compared to warfarin specifically on HF-related events. Given that patients with HFrEF frequently experience multiple HF hospitalizations (14), in this manuscript, we provide detailed analyses of both time to first and time to recurrent events.

Methods

Study Participants

Details of the WARCEF trial have been published previously(1). In this randomized, double-blind trial, 2,305 patients with left ventricular ejection fraction (LVEF) ≤ 35% in SR were randomly assigned to warfarin (target INR 2.75, with acceptable target range of 2.0 to 3.5) or aspirin (325 mg per day). Patients were enrolled at 168 centers in 11 countries between October 2002 and January 2010. The mean follow-up time was 3.5 years (SD 1.8 years). Patients who had a clear indication for warfarin or aspirin were not eligible. Additional eligibility criteria were a modified Rankin score of 4 or less (on a scale of 0 to 6, with higher scores indicating more severe disability), and planned treatment with a beta-blocker, an ACE inhibitor (or, if the side-effect profile with ACE inhibitors was unacceptable, with an ARB), or hydralazine and nitrates. Patients were ineligible if they had a condition that conferred a high risk of cardiac embolism, such as atrial fibrillation, a mechanical cardiac valve, endocarditis, or an intracardiac mobile or pedunculated thrombus.

Assessment of Outcomes and Major Adverse Events

In WARCEF, an independent end-point adjudication committee, whose members were unaware of the treatment assignments, adjudicated all primary and secondary outcomes and major hemorrhages. Heart failure hospitalizations were defined as hospital admissions 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. All deaths were first classified as cardiovascular or non-cardiovascular and cardiovascular deaths were further classified into other types. HF deaths were defined by the presence of at least one of the following at the time of death: 1) cardiogenic shock, 2) pulmonary edema, or 3) refractory HF (patient requiring continuous positive inotropic

therapy or mechanical circulatory assistance or experiencing HF symptoms at rest or requiring confinement to bed or a chair).

The current analyses are for the 489 WARCEF patients who experienced at least one HF-related event (HF hospitalization, HF death, or both)

Statistical Analysis

In the aspirin and warfarin groups, baseline characteristics for patients who experienced at least one HF-related event (HF hospitalization, HF death, or both) were compared using two-sample t-tests for continuous variables and Chi-squared tests for categorical variables. Comparisons of the percentages of patients in the two treatment groups who experienced at least one HF-related event used the exact test of two independent proportions, and comparisons of the rates used the exact conditional binomial test for two independent Poisson variables. We used Cox models to assess the effect of treatment on time to the first HF-related event, and extended these Cox models to accommodate time to recurrent events analysis using two modeling techniques. One, the total time conditional or Prentice-Williams-Peterson counting process (PWP-CP) model is conditional: only patients who have already experienced a prior HF-related event are included in the risk set for a next HF-related event (15). Thus the hazard ratio gives information on the effectiveness of treatment on the k^{th} HF-related event amongst patients who have undergone a previous event. In the other technique, the total time marginal model [Wei, Lin, and Weissfeld (WLW)], marginal Cox models are estimated for each event time. In the Cox model for the kth HF-related event, all patients remain in the analytic risk sets whether or not they previously experienced such events, until they either have a k^{th} event or are censored. Thus the hazard ratio associated with the k^{th} event from a marginal model is based on information from a larger group of patients than that from a conditional model, because the marginal model does not exclude patients without prior events. Robust sandwich estimators for standard errors were used to produce the p-values for the WLW models (16).

All of the above analyses were adjusted for variables found in univariable models to be predictive of at least one of the 5 events (first HF hospitalization, HF death, first HF hospitalization or death, recurrent HF hospitalization, recurrent HF hospitalization or HF death) [Supplemental Table 1]. The variables identified as predictive were age, continent from which patients were enrolled, body mass index, non-Hispanic white, systolic blood pressure, diabetes mellitus, hypertension, myocardial infarction, ischemic cardiomyopathy, peripheral vascular disease, prior stroke or transient ischemic attack, alcohol consumption, education, NYHA class III or IV, ejection fraction, 6-min walk, baseline MMSE score, baseline MLWHF score, already on warfarin or other oral anticoagulant, diuretics, ICD, BUN, eGFR, hemoglobin, sodium, and WBC. Multiple imputation was used to account for missing covariate data. We created five data sets using a sequential regression imputation method, performed Cox regression analyses on each data set, and subsequently combined the results to produce the reported hazard ratios and p-values using the method described by Rubin (17,18). The very few ties in the data were handled by replacing the continuous-time Cox partial likelihood function with Cox's discrete-time partial likelihood function. The analysis was performed in SAS with the TIES=DISCRETE option in the PROC PHREG

procedure. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

Results

Descriptive statistics are presented in Table 1. With the exception of a borderline difference in age (p=0.05), there were no significant differences between treatment groups in the baseline characteristics of patients experiencing at least one HF-related event.

Analysis of First Events

In unadjusted analyses of the 489 first HF hospitalization events, a significantly lower proportion of patients treated with aspirin had either at least one HF hospitalization or HF death (aspirin: 224, 19.3%; warfarin: 265 patients, 23.2%; OR=0.79, p=0.022); and aspirin also resulted in a significant risk reduction in time to first HF-related events [Table 2, unadjusted HR 0.82 (95% CI 0.69–0.98), p=0.031; However, after adjustment for baseline covariates there was no significant difference between the treatment groups in time to HF event [Table 2 adjusted HR 0.87 (95% CI 0.72–1.04), p=0.117].

Similarly, in unadjusted analyses of first HF hospitalization alone (451 events), fewer patients treated with aspirin (208, 17.9%) had at least one HF hospitalization, compared to 243 (21.3%) warfarin-treated patients (OR=0.81, p=0.041), and time-to-first HF hospitalization was marginally improved by aspirin compared to warfarin. [Table 2, unadjusted HR 0.83 (95%CI 0.69–1.00), p=0.052]. After adjustment, however, the difference between the treatment groups was not significant [adjusted HR 0.88 (95%CI 0.73–1.06), p=0.168].

There were 70 (6.0%) HF deaths in the aspirin-treated patients compared to 76 (6.7%) in the warfarin group (OR=0.90, p=0.550), with no significant difference in time to HF death [Table 2, Figure 1, unadjusted HR 0.93 (95%CI 0.67–1.28), p=0.639; adjusted HR 0.99 (95% CI 0.71–1.38), p=0.952]. This suggests no differential treatment effect on HF mortality, although the number of events is relatively small.

Analysis of All Events

In unadjusted analyses of all 1078 HF events, patients assigned to Aspirin had a lower rate of HF related events (hospitalizations or HR deaths) than patients assigned to warfarin. (Figure 2; aspirin: 502 events, 12.4 per 100 patient-years; warfarin: 576 events, 14.2 per 100 patient-years; rate ratio=0.87 (95% CI 0.77–0.99), p=0.028). There was also a significant difference between the overall unadjusted HF hospitalization rate (Figure 3) in the two treatment groups (aspirin 432 events, 10.7 per 100 patient-years; warfarin 500 events, 12.4 per 100 patient-years; rate ratio= 0.87 (95% CI 0.76–0.99), p=0.031.

Table 3 presents adjusted and unadjusted analyses of time to recurrent events from both the PWP-CP (conditional) and WLW (marginal) models, which give similar results. The conclusion for time to first HF event (hospitalization or death) stays the same: there is a significant benefit for aspirin before, but not after, adjustment for baseline covariates. There is no significant risk difference between aspirin and warfarin-treated patients in subsequent

events (2nd HF hospitalization or death and 3rd HF hospitalization or death), in both unadjusted and adjusted analyses.

The results for HF hospitalization alone show a marginally significant difference (p=0.051) in the unadjusted analysis for first event. Having noted this, there are no significant differences between warfarin and aspirin patients in either adjusted or unadjusted analyses of any of the recurrent HF hospitalization events, first or subsequent, under either the PWP-CP or the WLW model.

Discussion

The Warfarin/Aspirin Study in Heart Failure (WASH) and WATCH trials raised concern about the safety of aspirin use in the advanced HF population (NYHA Class III and IV) as both showed an increased risk of HF hospitalization rates for aspirin compared to warfarin (2,19). Although no mortality benefit was seen, in WASH there was a trend toward higher mortality in the aspirin group compared to the warfarin or placebo groups. Similarly, when analyzing the SOLVD treatment and prevention arms, there was a strong interaction between the use of antiplatelet agents and all-cause mortality in patients with HF and a reduced ejection fraction. Although patients with LV systolic dysfunction who received antiplatelet agents in addition to enalapril experienced a significant reduction in the combined end point of death or HF hospitalization compared to those randomized to placebo, this benefit was attenuated when compared to those patients who received enalapril in the absence of an antiplatelet agent (20).

There are mechanistic reasons and data to support the potentially detrimental effect of aspirin in patients with HF (21). The upregulation of prostaglandin synthesis and resulting vasodilatory effect may be an important mechanism to counteract various mediators of vasoconstriction in patients with HF (22). Aspirin has also been shown to reduce renal prostaglandin E2 and decrease renal sodium excretion as well as decreasing eGFR (23–25). By interfering with prostaglandin production, aspirin and other cyclooxygenase inhibitors may exert harm by blunting these vital compensatory responses.

On the other hand, in addition to causing platelet activation and aggregation, thromboxane A_2 directly causes vasoconstriction and is thought to mediate, at least in part, the vasoconstrictive effect of angiotensin II (26). In this case, selective inhibition of thromboxane production by aspirin may be beneficial in patients with HF. As a result of these complex and potentially contradictory downstream effects of aspirin in patients with HF, the potential clinical consequence of its use in this population is an important concern.

In this post-hoc analysis of the WARCEF data, which are much more extensive than WASH and WATCH combined (8,077 follow-up years for 2,305 patients in WARCEF compared to 3,383 follow-up years for 1,767 patients in the others combined), included both time to first event and all-event analyses. The results did not demonstrate an increased risk of HF hospitalization or HF death in patients receiving aspirin compared to those receiving warfarin in either analysis. Although the reason for the discrepancy between WARCEF and WATCH is not known, it bears emphasis that the results of WARCEF reflect a contemporary

trial of patients with systolic HF, where greater than 98%, 85%, 75% of patients were receiving an ACE inhibitor or ARB, a beta blocker, or a mineralocorticoid receptor antagonist, respectively. WARCEF provides important reassurance that the use of aspirin is not associated with an increase in clinically meaningful exacerbations of HF leading to hospitalization or an increase in death due to HF, when compared to patients who were receiving warfarin.

Study Limitations

As in all clinical trials, patients enrolled in WARCEF are a selected population of individuals that may not be representative of community dwelling HF populations and can limit the generalizability of these findings. Second, our analysis does not have the benefit of a placebo control group. While this would be ideal, it was not the design of the WARCEF trial. Given this, the comparison of aspirin to warfarin, which is randomized, is clinically meaningful, and suggests (but does not prove) that the use of aspirin is not associated with detrimental effects in terms of the clinical outcomes of patients with HFrEF. Third, it is useful to assess the precision of findings that are not statistically significant. Examining the upper confidence limits for first and second HF-related events in the marginal models in Table 3, we can rule out risk elevations above 5% (upper 95% CI for HR=1.05) for 1st HFHD; 15% for 2nd HFHD; 7% for 1st HFH; and 20% for 2nd HFH. (The results of the conditional model and for third HF-related events are less reliable). Fourth, we did not correct for multiple comparisons because we were not trying to ‘prove’ a positive post hoc finding, which would have required such adjustment. Given this, correction for multiple comparisons is unnecessary, and indeed, would only reinforce the null conclusions.

Conclusions

Among patients with HFrEF in the WARCEF trial, those who received aspirin experienced fewer HF events than those who received warfarin. After adjustment, however, there was no significant difference in risk between the aspirin and warfarin-treated patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

ACE	angiotensin converting enzyme
ARB	angiotensin receptor blocker
HF	heart failure

HFrEF	heart failure with reduced ejection fraction (HFrEF)
LVEF	left ventricular ejection fraction
SR	sinus rhythm
WARCEF	Warfarin Aspirin Reduced Cardiac Ejection Fraction trial

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Perspectives

Competency in Medical Knowledge

Despite mechanistic reasons and prior trial results raising a concern that aspirin may result in an increased risk of HF hospitalization and higher mortality in patients with HFrEF on an ACE inhibitor or ARB, the use of aspirin was no associated with an increased risk of heart failure hospitalization or death compared to warfarin in WARCEF.

Translational Outlook

Further randomized, placebo controlled studies could address the potential hazard of aspirin use in addition to an ACE inhibitor or ARB in patients with HFrEF.

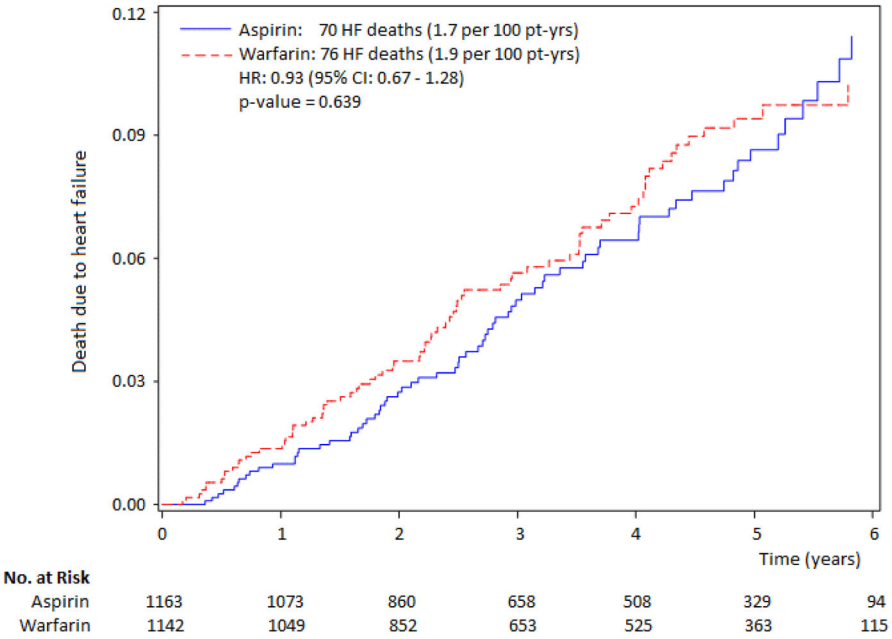

Figure 1.
Kaplan-Meier curves of death due to heart failure

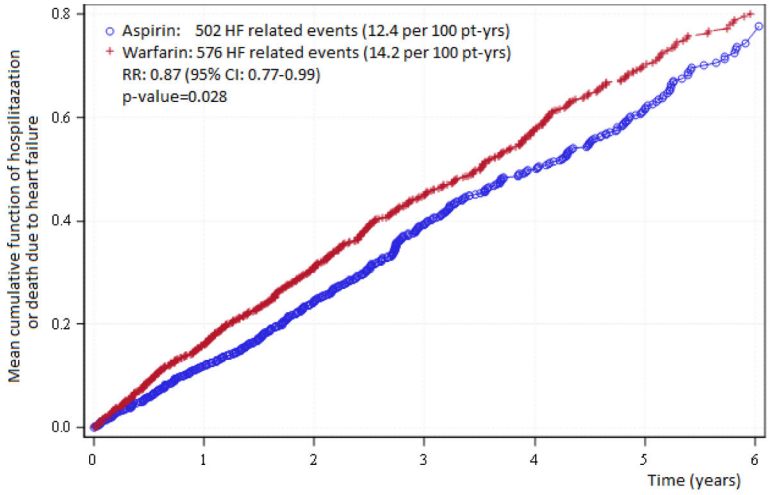

Figure 2.
Mean cumulative function curves for HF-related events (hospitalization or death)

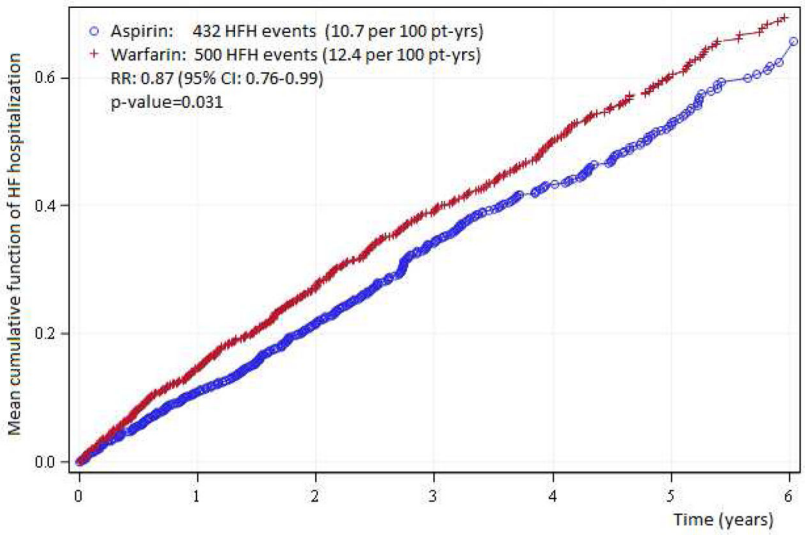

Figure 3.
Mean cumulative function curves of HF hospitalization.

Table 1

Comparison of baseline characteristics by treatment group for patients who experienced heart failure death or at least one heart failure hospitalization

Characteristics	Aspirin (n=224)	Warfarin (n=265)	p-value
Age - yr	60.2±11.7	62.2± 11.8	0.050
Location			0.246
AR	2/224 (0.9)	8/265 (3.0)	.
EU	95/224 (42.4)	107/265 (40.4)	.
NA	127/224 (56.7)	150/265 (56.6)	.
Male sex	187/224 (83.5)	214/265 (80.8)	0.434
Race or ethnic group			0.757
Non-Hispanic white	157/224 (70.1)	196/265 (74.0)	.
Non-Hispanic black	47/224 (21.0)	48/265 (18.1)	.
Hispanic	15/224 (6.7)	17/265 (6.4)	.
Other	5/224 (2.2)	4/265 (1.5)	.
Height - cm	172.4± 9.2	171.7± 9.6	0.273
Weight - kg	88.1± 18.6	86.0± 21.7	0.065
Body-mass index - Mean	29.7± 6.4	29.0± 6.4	0.134
Systolic blood pressure - mmHg	121.4± 18.8	119.4± 19.6	0.326
Diastolic blood pressure - mmHg	73.6± 11.6	72.0± 12.3	0.118
Pulse - beats/min	74.4± 13.7	73.7± 11.3	0.692
Hypertension	131/214 (61.2)	154/260 (59.2)	0.661
Diabetes Mellitus	88/223 (39.5)	102/265 (38.5)	0.826
Atrial Fibrillation	10/223 (4.5)	13/265 (4.9)	0.827
Myocardial Infarction	112/223 (50.2)	134/265 (50.6)	0.940
Ischemic Cardiomyopathy	115/223 (51.6)	127/265 (47.9)	0.422
Pulmonary or other embolism	5/223 (2.2)	10/265 (3.8)	0.329
Peripheral Vascular Disease	35/224 (15.6)	38/265 (14.3)	0.691
Prior stroke or TIA	34/223 (15.2)	42/265 (15.8)	0.855
Smoking status			0.742
Current smoker	43/224 (19.2)	45/265 (17.0)	.
Former smoker	118/224 (52.7)	148/265 (55.8)	.
Never smoked	63/224 (28.1)	72/265 (27.2)	.
Alcohol Consumption			0.421
Current consumption, >2 oz/day	39/224 (17.4)	58/265 (21.9)	.
Previous consumption, >2 oz/day	62/224 (27.7)	65/265 (24.5)	.
Never consumed alcohol	123/224 (54.9)	142/265 (53.6)	.
Educational level			0.146
< High school	89/223 (39.9)	116/265 (43.8)	.
High-school graduate or some college	96/223 (43.0)	120/265 (45.3)	.

Characteristics	Aspirin (n=224)	Warfarin (n=265)	p-value
College graduate or postgraduate	38/223 (17.0)	29/265 (10.9)	.
NYHA classification			0.904
1	22/222 (9.9)	22/264 (8.3)	.
2	106/222 (47.7)	132/264 (50.0)	.
3	91/222 (41.0)	107/264 (40.5)	.
4	3/222 (1.4)	3/264 (1.1)	.
Ejection fraction - %	23.5± 7.2	22.8± 7.0	0.338
6-minute walk distance - m	316.5±135.9	324.4±142.1	0.734
Baseline MLWHF score	41.9± 25.6	39.8± 23.8	0.361
Medications			
Aspirin	126/204 (61.8)	141/250 (56.4)	0.248
Other antiplatelet agent	7/50 (14.0)	8/71 (11.3)	0.653
Warfarin or other oral anticoagulant	28/224 (12.5)	22/265 (8.3)	0.127
ACE inhibitor or ARB	221/224 (98.7)	260/264 (98.5)	1.000
Beta-blocker	199/224 (88.8)	228/264 (86.4)	0.410
Mineralocorticoid Receptor Antagonist	87/108 (80.6)	108/141 (76.6)	0.452
Nitrate	61/224 (27.2)	73/264 (27.7)	0.918
Calcium-channel blocker	20/224 (8.9)	24/264 (9.1)	0.950
Diuretic	205/224 (91.5)	239/264 (90.5)	0.704
Statin	138/149 (92.6)	156/178 (87.6)	0.137
Implantable cardioverter–defibrillator	41/223 (18.4)	65/265 (24.5)	0.101
eGFR	65.5±20.5	63.8±21.6	0.300
Hemoglobin - g/dL	14.0±1.7	13.8±1.7	0.340
Sodium - mEq/L	139.5±3.8	139.0±3.6	0.148

Table 2

Time to first event by treatment group

	No. of events (cumulative event rate, KM%)		Unadjusted		Adjusted*	
Outcome	**Aspirin (n=1163)**	**Warfarin (n=1142)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
HF hospitalization or HF death	224 (27.9%)	265 (31.8%)	0.82 (0.69, 0.98)	**0.031**	0.87 (0.72, 1.04)	0.117
HF hospitalization	208 (26.0%)	243 (29.3%)	0.83 (0.69, 1.00)	0.052	0.88 (0.73, 1.06)	0.168
HF death	70 (11.4%)	76 (10.2%)	0.93 (0.67, 1.28)	0.639	0.99 (0.71, 1.38)	0.952

*Adjusted for variables that are predictive of at least one of the 5 events (first HF hospitalization, HF death, first HF hospitalization or death, recurrent HF hospitalization, recurrent HF hospitalization or death) in univariable models: Age, Continent, Body Mass Index, Non-Hispanic White, Systolic Blood Pressure, Diabetes Mellitus, Hypertension, Myocardial Infarction, Ischemic Cardiomyopathy, Peripheral Vascular Disease, Prior Stroke or TIA, Alcohol consumption, Education, NYHA Class III or IV, Ejection Fraction, 6-min Walk, Baseline Mini-Mental Status Examination Score, Baseline Minnesota Living with Heart Failure Score, On Warfarin or Other Oral Anticoagulant at baseline, Diuretic Use, Implantable Cardiac Defibrillator, Blood Urea Nitrogen, Estimated Glomerular Filtration Rate, Hemoglobin, Sodium, and White Blood Cell Count.

Table 3

Time-to-recurrent event analysis for HF events

			Total Time Conditional Model				Total Time Marginal Model*			
	No. of events		Unadjusted		Adjusted†		Unadjusted		Adjusted†	
	Aspirin (n=1163)	Warfarin (n=1142)	HR(95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
1st HFHD§	224	265	0.82 (0.69, 0.98)	**0.031**	0.86 (0.72, 1.03)	0.094	0.82 (0.69, 0.98)	**0.031**	0.87 (0.72, 1.05)	0.143
2nd HFHD	116	137	1.10 (0.86, 1.41)	0.449	1.18 (0.92, 1.53)	0.194	0.84 (0.66, 1.07)	0.165	0.90 (0.70, 1.15)	0.397
3rd HFHD	68	73	1.24 (0.88, 1.74)	0.222	1.36 (0.96, 1.93)	0.087	0.93 (0.67, 1.30)	0.678	1.00 (0.72, 1.40)	0.982
1st HFH‡	208	243	0.83 (0.69, 1.00)	0.051	0.87 (0.72, 1.05)	0.141	0.83 (0.69, 1.00)	0.051	0.88 (0.73, 1.07)	0.202
2nd HFH	101	117	1.13 (0.86, 1.47)	0.387	1.20 (0.91, 1.58)	0.190	0.86 (0.66, 1.12)	0.250	0.92 (0.70, 1.20)	0.522
3rd HFH	54	58	1.23 (0.84, 1.80)	0.286	1.35 (0.92, 2.00)	0.128	0.93 (0.64, 1.35)	0.707	1.01 (0.69, 1.46)	0.979

*Robust sandwich estimators for standard errors were used to produce the p-values from the marginal models.

†Adjusted for variables that are predictive of at least one of the 5 events (first HFH, HF Death, first HFH or Death, recurrent HFH, recurrent HFH or Death) in univariable models: Age, Continent, Body Mass Index, Non-Hispanic White, Systolic Blood Pressure, Diabetes Mellitus, Hypertension, Myocardial Infarction, Ischemic Cardiomyopathy, Peripheral Vascular Disease, Prior Stroke or TIA, Alcohol consumption, Education, NYHA Class III or IV, Ejection Fraction, 6-min Walk, Baseline Mini-Mental Status Examination Score, Baseline Minnesota Living with Heart Failure Score, On Warfarin or Other Oral Anticoagulant at baseline, Diuretic Use, Implantable Cardiac Defibrillator, Blood Urea Nitrogen, Estimated Glomerular Filtration Rate, Hemoglobin, Sodium, and White Blood Cell Count.

‡HFH= Heart Failure Hospitalization

§HFHD= HF Hospitalization or Death