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Warfarin Use and Outcomes in Patients with Advanced Chronic Systolic Heart Failure without Atrial Fibrillation, Prior Thromboembolic Events, or Prosthetic Valves

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Abstract

Warfarin is often used in systolic heart failure (HF) patients to prevent adverse outcomes. However, its long term effect remains controversial. The objective of this study was to determine the association of warfarin use and outcomes in advanced chronic systolic HF patients without atrial fibrillation (AF), previous thromboembolic events or prosthetic valves. Of the 2708 BEST patients, 1642 were free of AF, without history of thromboembolic events and without prosthetic valves at baseline. Of these, 471 (29%) patients were receiving warfarin. Propensity scores for warfarin use were estimated for each patient and were used to assemble a matched cohort of 354 pairs of patients with and without warfarin use, who were balanced on 62 baseline characteristics. Kaplan-Meier and Cox regression analyses were used to estimate the association between warfarin use and outcomes during 4.5 years of follow-up. Matched participants had a mean (SD) age of 57 (13) years with 24% women and 24% African Americans. All-cause mortality occurred in 30% of matched patients in both groups receiving and not receiving warfarin (hazard ratio, 0.86; 95% confidence interval, 0.62–1.19; P=0.361). Warfarin use was not associated with cardiovascular mortality (hazard ratio, 0.97; 95% confidence interval, 0.68–1.38; P=0.855) or HF hospitalization (hazard ratio, 1.09; 95% confidence interval, 0.82–1.44; P=0.568). In conclusion, in chronic

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advanced systolic HF patients without AF or other recommended indications for anticoagulation, the prevalence of warfarin use was relatively high. However, despite therapeutic INR among those receiving warfarin, its use had no significant intrinsic association with mortality and hospitalization.

Keywords

heart failure; warfarin; mortality; hospitalization

Heart failure (HF) is a hypercoagulable state, and HF patients with low left ventricular ejection fraction (LVEF) may be at increased risk of left ventricular (LV) thrombus formation and thromboembolic events.^{1–3} Although the use of anticoagulants is recommended in HF patients with atrial fibrillation (AF) and/or a previous thromboembolic event,⁴ there is conflicting evidence of the benefit of anticoagulation use in HF patients without AF and/or previous thromboembolic events.^{5–10} However, as the risk of LV thrombus formation increases with decreasing LVEF, clinicians are often concerned about the risk of LV thrombus formation in their HF patients with markedly low LVEF. The objective of the current study is to determine the association of warfarin use and outcomes in advanced chronic systolic HF patients without AF and/or previous thromboembolic events.

Methods

We conducted a post-hoc analysis of the public-use copy of the Beta-Blocker Evaluation of Survival Trial (BEST) data for the current study. The BEST was a multicenter randomized placebo-controlled clinical trial of bucindolol, a beta-blocker, in HF, the methods and results of which have been previously published.¹¹ Briefly, 2708 patients with advanced chronic systolic HF were enrolled from 90 different sites across the United States and Canada between May 1995 and December 1998. All but one patient consented to be part of the public-use copy of the data. At baseline, patients had a mean duration of 49 months of HF and had a mean left ventricular ejection fraction (LVEF) of 23%. All patients had New York Heart Association (NYHA) class III–IV symptoms and over 90% of all patients were receiving angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digitalis.

Data on use of warfarin at baseline was available on all 2707 participants. For our current analysis, we excluded 692 patients with AF, 343 patients with history of thromboembolic diseases and 30 patients with prosthetic valves at baseline. Thus our final sample size was 1642, of which, 471 (29%) patients were receiving warfarin at baseline. Considering the significant imbalances in baseline characteristics between the two groups (Table 1), we used propensity scores to assemble a matched cohort of 354 pairs of patients who were well-balanced on 62 baseline characteristics.^{12–18} Propensity scores for warfarin use were estimated for each of the 1642 patients using a non-parsimonious multivariable logistic regression model.^{19, 20} Absolute standardized differences were estimated to evaluate the pre-match imbalance and post-match balance, and presented as a Love plot. An absolute standardized difference of 0% indicates no residual bias and differences <10% are considered inconsequential.

BEST participants were followed up for a minimum of 18 months and a maximum of 4.5 years.¹¹ Primary outcomes for the current analysis was all-cause mortality during 4.1 years of follow-up (mean, 2 years; range, 10 days to 4.14 years). Secondary outcomes were cardiovascular and HF mortality, and all-cause and HF hospitalization. Kaplan-Meier and Cox regression analyses were used to determine associations between warfarin use and outcomes during 4.1 years of follow-up. Log-minus-log scale survival plots were used to

check proportional hazards assumptions. Subgroup analyses were conducted to determine the homogeneity of association between use of warfarin and all-cause mortality. All statistical tests were two-tailed with a p-value <0.05 considered significant. All data analyses were performed using SPSS for Windows version 18 (SPSS Inc., Chicago, IL).

Results

Matched patients had a mean (SD) age of 57 (13) years, 170 (24%) were women and 171 (24%) were African Americans. Before matching, patients receiving warfarin were younger, had a lower mean of left and right ventricular ejection fraction, a lower prevalence of hypertension, diabetes mellitus but had a higher symptom burden such as jugular venous distension, S3 gallop. These and other imbalances in baseline characteristics were well balanced after matching (Table 1 and Figure 1). After matching, absolute standardized differences for all measured covariates were <10% (most were <5%), suggesting substantial covariate balance across the groups (Figure 1). Median INR (interquartile range) were 2.0 (1.1) and 1.0 (0.1) for matched patient receiving and not receiving warfarin respectively.

Overall, 212 (30%) matched patients died from all causes during a 2.1 years of median follow-up. All-cause mortality occurred in 30% and 30% of matched patients receiving and not receiving warfarin respectively (hazard ratio, 0.86, 95% confidence interval, 0.62 1.19; P=0.361 Figure 2 and Table 2). The association between warfarin use and all-cause mortality was homogenous across a wide spectrum of participants, including those with LVEF $\leq$ 20% and >20% (Figure 3). When we used LVEF as a continuous variable, we still did not observe any statistically significant interaction between use of warfarin and LVEF (p for interaction, 0.815). Pre-match unadjusted, multivariable-adjusted and propensity score adjusted hazard ratio between warfarin and no-warfarin use among the 1642 pre-match patients are displayed in Table 2. Warfarin had no association with cardiovascular and heart failure mortality, and all-cause and heart failure hospitalization after matching (Table 3).

Discussion

Findings from the current study demonstrate that in patients with advanced chronic systolic HF without AF and/or previous thromboembolic events, the prevalence of warfarin use was relatively high. Nevertheless, our data suggest that despite achieving a mean therapeutic INR, warfarin use did not provide any intrinsic survival benefit in patients with advanced chronic systolic HF who had no other established indications for anticoagulation. These findings are important because many practicing physicians perceive advanced chronic systolic HF as a pre-thrombotic stage and prescribe warfarin, even though current ACC/AHA guidelines have no clear recommendation on this.⁴ Thus, it is possible that warfarin may be prescribed without any proven benefit and with the potential increased risk of bleeding and other adverse effects.²¹

The unadjusted association of warfarin use with increased risk of cardiovascular mortality is rather surprising given that pre-match patients receiving warfarin were younger, had lower or similar baseline prevalences of cardiovascular comorbidities (Table 1). These suggest strong confounding by a history of ventricular fibrillation, higher symptom burden, and lower mean LVEF and RVEF, all of which are known to increase risk of cardiovascular death. The near significant unadjusted association between warfarin use and sudden cardiac death is likely due to increased prevalence of ventricular fibrillation among warfarin users. Despite a higher burden of HF symptoms among warfarin users, the lack of significant unadjusted associations of warfarin use with HF mortality and HF hospitalization are intriguing, but may suggest that LVEF and HF symptoms were rather weak confounders.

The lack of significant associations of warfarin use with mortality and hospitalization among matched patients suggests lack of an intrinsic effect of warfarin on outcomes in patients with advanced systolic HF without AF and/or thromboembolic disorders. Although a low LVEF is often considered an indication for warfarin use in these patients, findings from our subgroup analysis suggest that the association between warfarin use and all-cause mortality was similar regardless of LVEF categories. The lack of an intrinsic effect of warfarin in advanced systolic HF patients without AF and/or thromboembolic events, despite a therapeutic INR, suggest that thromboembolic events may not underlie mechanisms of death or hospitalization in these patients. Findings from our study provide further evidence supporting the current guideline recommendations that the use of warfarin in HF patients should be restricted to those with AF and/or previous thromboembolic events.⁴

There is conflicting evidence in the literature regarding the role of warfarin in patients with advanced systolic HF without atrial fibrillation or other indications for anticoagulation.^{5, 22} In one study warfarin use was associated with reduced mortality and morbidity in mild to moderate (two third had NYHA class I–II symptoms) chronic systolic HF patients.⁷ Our study is distinguished by more advanced HF patients (all NYHA III–IV symptoms) and the use of propensity-matched design that allowed the assembly of a balanced cohort. Findings from our study are consistent with those from the largest randomized clinical trial of anticoagulation in HF patients with normal sinus rhythm to date in which there was no difference in outcomes between patients receiving warfarin (open label), aspirin or clopidogrel.⁹ However this study was not considered definitive since it was terminated prematurely because of slow enrollment resulting in estimated power of only 40% to detect 20% difference. In the absence of another large clinical trial with adequate power, observational studies such as ours adds further evidence of lack of benefit for therapeutic anticoagulation in these patients.

As in all observational studies, a key limitation of our study is potential confounding by an unmeasured covariate. A sensitivity analysis would normally help quantify the degree of a hidden bias that would need to be present to invalidate conclusions based on significant associations in an observational study. However, sensitivity analyses can only be performed if the observed association is statistically significant.²³ Another limitation is lack of data on other cardiovascular events including stroke and adverse events such as bleeding. In conclusion, in patients with advanced chronic systolic HF without AF and/or other indications for anticoagulation, despite a mean INR which was therapeutic, the use of warfarin was not associated with clinical outcomes.

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Figure 1.

Absolute standardized differences comparing covariate values for patients with and without warfarin use, before and after propensity score matching (LVEF=left ventricular; NYHA= New York Heart Association; RVEF=right ventricular)

Number of patients at risk

No Warfarin	354	272	180	84	4
Warfarin	354	295	211	95	11

Figure 2.
Kaplan-Meier plots for all-cause mortality by use of warfarin (CI=confidence interval;
HR=hazard ratio)

Figure 3. Association of use of warfarin and all cause mortality in subgroups of matched patients (CI=confidence interval; HR=hazard ratio)

Table 1

Baseline patient characteristics by use of warfarin, before and after propensity matching

n (%) or mean (±SD) Variable	Before propensity matching			After propensity matching		
	No warfarin (n=1171)	Warfarin (n=471)	P value	No warfarin (n=354)	Warfarin (n=354)	P value
Age (years)	60 (± 12)	56 (± 12)	<0.001	57 (±14)	57 (± 12)	0.353
Female	283 (24%)	107 (23%)	0.532	87 (25%)	83 (23%)	0.781
African American	302 (26%)	108 (23%)	0.226	84 (24%)	87 (25%)	0.857
Current smoking	213 (18%)	94 (20%)	0.406	73 (21%)	68 (19%)	0.709
Body mass index (kg/m ²)	37 (±9)	37 (±8)	0.643	37 (±9)	37 (±8)	0.446
NYHA class III	1086 (93%)	429 (91%)	0.255	322 (91%)	327 (92%)	0.583
Past medical history						
Heart failure duration (months)	46 (± 48)	44 (± 44)	0.505	45 (± 47)	45 (± 45)	0.939
Coronary artery disease	670 (57%)	265 (56%)	0.724	190 (54%)	192 (54%)	0.937
Angina pectoris	624 (53%)	238 (51%)	0.312	172 (49%)	178 (50%)	0.708
Hypertension	715 (61%)	239 (51%)	<0.001	191 (54%)	191 (54%)	1.000
Diabetes mellitus	452 (39%)	156 (33%)	0.038	124 (35%)	118 (33%)	0.693
Hyperlipidemia	527 (45%)	208 (44%)	0.756	145 (41%)	149 (42%)	0.825
Ventricular fibrillation	79 (7%)	54 (12%)	0.002	31 (9%)	33 (9%)	0.896
Peripheral vascular disease	164 (14%)	78 (17%)	0.186	53 (15%)	52 (15%)	1.000
Medications						
Bucindolol	600 (51%)	229 (49%)	0.337	168 (48%)	172 (49%)	0.821
ACE inhibitors /ARB	1137 (97%)	458 (97%)	0.875	340 (96%)	345 (98%)	0.425
Digitalis	1056 (90%)	449 (95%)	0.001	333 (94%)	334 (94%)	1.000
Diuretics	1086 (93%)	433 (92%)	0.573	326 (92%)	327 (92%)	1.000
Vasodilators	504 (43%)	204 (43%)	0.920	146 (41%)	150 (42%)	0.818
Aspirin	738 (63%)	98 (21%)	<0.001	91 (26%)	96 (27%)	0.640
Statins	273 (23%)	117 (25%)	0.511	87 (25%)	83 (23%)	0.794
Physical examination						
Pulse (beats per minute)	82 (±13)	83 (±13)	0.100	83 (±13)	83 (±13)	0.979
Systolic BP (mm Hg)	119 (±19)	114 (±16)	<0.001	115 (±16)	115 (±16)	0.708
Diastolic BP (mm Hg)	72 (±11)	71 (±11)	0.114	72 (±11)	71 (±11)	0.738

n (%) or mean (±SD) Variable	Before propensity matching			After propensity matching		
	No warfarin (n=1171)	Warfarin (n=471)	P value	No warfarin (n=354)	Warfarin (n=354)	P value
Jugular venous distension	399 (42%)	836 (48%)	0.003	134 (38%)	147 (42%)	0.356
S3 gallop	477 (41%)	240 (51%)	<0.001	165 (47%)	173 (49%)	0.582
Pulmonary rales	162 (14%)	38 (8%)	0.001	36 (10%)	35 (10%)	1.000
Hepatomegaly	115 (10%)	46 (10%)	0.973	36 (10%)	39 (11%)	0.807
Edema	288 (25%)	96 (20%)	0.068	76 (22%)	74 (21%)	0.924
Laboratory data						
Hemoglobin (g/dL)	13.9 (±1.6)	14.2 (±1.6)	0.003	14.0 (±1.6)	14.1 (±1.6)	0.522
Serum creatinine (mg/dL)	1.2 (±0.4)	1.2 (±0.4)	0.722	1.2 (±0.4)	1.2 (±0.4)	0.808
Serum potassium (mEq/L)	4.34 (±0.46)	4.29 (±0.47)	0.046	4.31 (±0.47)	4.31 (±0.46)	0.807
Plasma norepinephrine, (pg/mL)	484 (±272)	524 (±321)	0.011	511 (±325)	509 (±302)	0.917
Partial thromboplastin time (in seconds)	28 (±8)	34 (±8)	<0.001	29 (±13)	34 (±7)	<0.001
International normalized ratio	1.1 (±0.3)	2.2 (±1.0)	<0.001	1.1 (±0.5)	2.2 (±0.9)	<0.001
Left bundle branch block by electrocardiogram	303 (26%)	124 (26%)	0.850	98 (28%)	94 (27%)	0.796
Cardiothoracic ratio by chest x-ray	54.8 (±7.2)	55.5 (±6.9)	0.101	55.1 (±7.3)	55.4 (±6.9)	0.590
Pulmonary edema by chest x-ray	114 (10%)	51 (11%)	0.505	37 (11%)	36 (10%)	1.000
Left ventricular ejection fraction by nuclear scan (%)	23.5 (±7.2)	21.4 (±7.3)	<0.001	22.4 (±7.5)	22.1 (±7.2)	0.520
Right ventricular ejection fraction by nuclear scan (%)	35.5 (±11.7)	33.6 (±12.5)	0.003	33.7 (±11.9)	34.1 (±12.4)	0.660

ACE=angiotensin converting enzyme; ARB= Angiotensin receptor blocker; BP= blood pressure; MI= Myocardial infarction.

Table 2

Effects of warfarin on all cause mortality in BEST trial

Outcomes	Events (%)		Absolute risk increase *	Hazard ratio (95% confidence interval)	P value
	No warfarin (n=1171)	Warfarin (n=471)			
Pre-match					
Unadjusted	321 (27%)	159 (34%)	+ 7%	1.20 (0.99 – 1.45)	0.062
Multivariable-adjusted **	---	---	---	1.14 (0.91 – 1.43)	0.253
Propensity-adjusted	---	---	---	1.08 (0.87 – 1.35)	0.477
Post-match					
	No warfarin (n=354)	Warfarin (n=354)			
All cause mortality	106 (30%)	106 (30%)	0%	0.86 (0.62 – 1.19)	0.361

* Absolute rate increase was calculated by subtracting the rates of events in the group receiving from those not receiving warfarin (before values were rounded)

** Multivariable model includes all the covariates displayed in the Figure 1

Table 3

Effects of warfarin on other outcomes in BEST trial.

Outcomes	Events (%)		Absolute risk increase*	Hazard ratio (95% confidence interval)	P value
	No warfarin (n=1171)	Warfarin (n=471)			
Before matching					
Cardiovascular mortality	268 (23%)	143 (30%)	+ 7%	1.29 (1.06 – 1.58)	0.013
Sudden cardiac death	151 (13%)	81 (17%)	+ 4%	1.31 (1.00 – 1.71)	0.052
Heart failure mortality	91 (8%)	45 (10%)	+ 2%	1.19 (0.83 – 1.70)	0.336
All cause hospitalization	702 (60%)	291 (62%)	+ 2%	0.99 (0.86 – 1.14)	0.883
Heart failure hospitalization	412 (35%)	186 (40%)	+ 5%	1.13 (0.95 – 1.34)	0.174
After matching					
	No warfarin (n=354)	Warfarin (n=354)			
Cardiovascular mortality	84 (24%)	95 (27%)	+ 3%	0.97 (0.68 – 1.38)	0.855
Heart failure mortality	27 (8%)	31 (9%)	+1%	0.73 (0.38 – 1.39)	0.332
All cause hospitalization	217 (61%)	225 (64%)	+ 3%	0.96 (0.76 – 1.22)	0.763
Heart failure hospitalization	131 (37%)	141 (40%)	+ 3%	1.09 (0.82 – 1.44)	0.568

* Absolute rate increase was calculated by subtracting the rates of events in the group receiving from those not receiving warfarin (before values were rounded)